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Symposium on the chemoprophylaxis of infection
I. Introduction and general principles

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IT IS of course, eminently logical to attempt to prevent any disease, regardless of cause, rather than to treat it after it has become clinically manifest. Preventive medicine has been most vigorously practiced in the broad field of infectious diseases; the control of diphtheria, smallpox, tetanus, and poliomyelitis, to mention a few, by immunologic means is evidence of the success of the preventive approach. Similarly, a number of illnesses caused by enteric pathogens can be prevented by the pasteurization of milk, purification of water, and adequate disposal of sewage. With the advent of antibiotics another potent weapon to prevent infections seemed at hand. There is no doubt that these agents have been responsible for eliminating mortality and alleviating morbidity in a multitude of bacterial infections. However, the mere fact that the antimicrobials have been effective in the eradication of bacterial pathogens which have already produced disease does not necessarily imply that these agents can prevent invasion of the host by pathogenic bacteria. Nevertheless, the tacit assumption has been made that this is the case, and it has been estimated that close to three fourths of the antibiotics prescribed in medical practice are given to

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Fig. 1. Some uses and abuses of antibiotic prophylaxis: *top left,* penicillin instilled into infant's eyes will almost surely prevent gonococcal ophthalmia; *top center,* penicillin administered to protect this child from the bacterial complications of measles is not likely to be effective; *top right,* prophylactic sulfonamides will abort the spread of meningococcal infection.

Lower left, a patient having an appendectomy is "covered" with antibiotics, an unnecessary and potentially dangerous practice; *lower center,* antibiotics are of no value in patients with indwelling urethral catheters; and *lower right,* prophylactic antimicrobials have failed to protect unconscious patients from pulmonary infections.

prevent rather than *treat* infections. It is the purpose of this brief review to examine critically the indications for the prophylactic use of antibiotics and to determine whether this practice is justified. A re-examination of this problem seems in order since it has become quite clear that administration of antibiotics is not without some danger to the patient.

Antibiotic prophylaxis is an integral part of everyday living, and is in force from the "cradle to the grave" (Fig. 1). For example, as soon as the newborn has emitted his first cry, penicillin is instilled into his eyes to prevent gonococcal ophthalmia. If the baby is premature, antibiotics are administered systemically to protect a "vulnerable host" from infection. The discovery of a staphylococcal carrier among the nursery personnel or the appearance of a breast abscess in the mother of a newborn may result in antibiotic feeding to the entire nursery. With this as a starting point, the antimicrobials almost become a staple in the diet of many children and, in addition to the treatment of overt bacterial disease, are employed to prevent bacterial complications of the common exanthems, particularly of measles and chickenpox. Even more frequently the common cold is considered an indication for the use of antibiotics.

When the child matriculates in school he is exposed to a new microbial flora which occasionally gives rise to epidemic outbreaks of disease. This flora consists predominantly of the hemolytic streptococcus, meningococcus, and occasionally, in closed environments, various enteric pathogens. Antimicrobial prophylaxis has been of distinct benefit in containing the spread of epidemic illness caused by these organisms. It should be emphasized, however, that the relative

quantity of antibiotics directed at these specific pathogens is miniscule compared to the prodigious amount used in the prevention of "bacterial complications" in ill-defined respiratory infections, or after operations, traumatic injuries, and burns, or to protect the susceptible host with chronic illness, such as cystic fibrosis or paralytic poliomyelitis, from invasion by bacterial pathogens.

This problem becomes magnified as life progresses and degenerative diseases make their appearance. In many patients with well-compensated chronic problems such as bronchitis and emphysema, cardiac failure, and diabetes mellitus, the progression of the disease is accelerated following intercurrent infections. Certainly prevention of infections in this group of patients might well prolong life. More importantly, the frequency with which pulmonary infections cause death in geriatric patients following acute vascular accidents needs no reiteration. It would not seem unreasonable to forestall the development of pneumonia in these patients by the use of antibiotics. Finally, it has become accepted practice, particularly in the geriatric age group, to "cover" with antibiotics patients who are subjected to such foreign bodies as urethral catheters, tracheostomy tubes, and sutures. This practice stems largely from the experience that such patients are prone to develop infections at the site of the foreign body.

The examples cited represent just a fraction of the conditions under which antibiotics are employed prophylactically. In most of these situations, the practice of administering these drugs has become "routine" and has not been studied under controlled conditions. Where such studies have been performed, the data indicate that antibiotic prophylaxis has been effective when directed at a *single* pathogen (Fig. 2). A prime example of this is the marked diminution in rheumatic fever following the institution of antistreptococcal control programs. Epidemics of meningococcal disease, gonorrhea, and shigellosis have also been eradicated by administration of the proper antibiotic to the susceptible population. Even when aimed at a single bacterial species, antibiotic prophylaxis is subject to a number of variables including the immune status of the host, the habitat of the microorganisms, and the time interval between exposure to the parasite and institution of chemotherapy. These relationships have

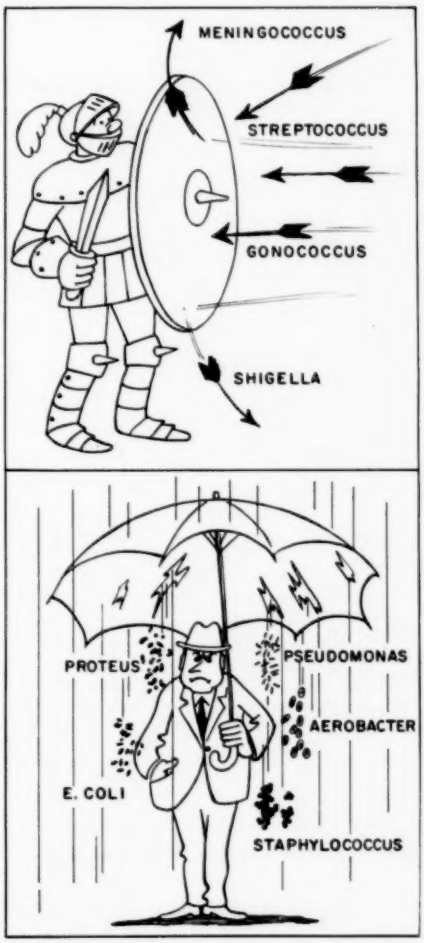

Fig. 2. When the proper antibiotic is intended to shield the host from invasion by a *single* pathogen, prophylaxis is likely to be effective. In contrast, attempts to use antibiotics as an umbrella over "infection-prone" patients frequently result in infections with a more resistant flora such as *Staphylococcus pyogenes, E. coli,* Pseudomonas, Aerobacter, and Proteus.

Table I. Use of prophylactic antimicrobials

- I. Antibiotics directed at specific pathogens
  - A. Suppression of overt disease following definite infection
    1. Scrub typhus
    2. Q fever
    3. Tularemia
    4. Typhoid fever
  - B. Prevention of disease following potential infection
    1. Meningococcal infections
    2. Enteric pathogens
       a. Shigellosis
       b. Amebiasis
       c. Pathogenic *E. coli*
    3. Gonococcal infections
    4. Staphylococcal disease in nurseries for newborn infants
  - C. Prophylaxis of poststreptococcal sequelae
    1. Prevention of acute streptococcosis
    2. Prevention of streptococcal recurrences in patients who have had rheumatic fever or nephritis
  - D. Prevention of bacterial endocarditis
- II. Antibiotics employed to protect susceptible patients from infection
  - A. Premature infants
  - B. Prevention of bacterial complications of acute nonbacterial diseases
    1. Upper respiratory infections
    2. Acute exanthems
    3. Surgery or major trauma
    4. Burns
    5. Complications of pregnancy
    6. Acute heart failure
    7. Paralytic poliomyelitis
    8. Comatose patients
  - C. Prophylaxis in chronic disease
    1. Cystic fibrosis
    2. Chronic bronchitis
    3. Chronic congestive heart failure
    4. Diabetes mellitus
    5. Neoplastic disease
    6. Chronic renal disease
  - D. Patients with alterations in resistance
    1. Receiving adrenal cortical hormones
    2. Leukopenia

been carefully studied in scrub typhus, Q fever, and tularemia, and will be discussed subsequently.

As has been mentioned, in most instances antibiotics are used prophylactically not against a specific microorganism but to protect the host from invasion by a variety of bacteria. In other words, the antibiotics constitute an umbrella to shield "infection-prone" patients. Only rarely has this practice been scrutinized critically; in fact, the few available studies suggest that the antibiotic umbrella usually leaks (Fig. 2).[1-4] In addition, most antibiotics have at least three disadvantages: in the first place, these agents are often the cause of toxic or allergic reactions; second, their use may be attended by the hazard of superinfections with more resistant bacterial species; and finally, they are expensive, particularly when given over a prolonged time. When these potential hazards are considered in the light of observations that antimicrobials used in prophylaxis are not nearly as effective as in therapy, the entire problem merits thorough re-evaluation.

Some of the clinical situations in which antibiotics have been employed for prophylaxis and which will be reviewed are summarized in Table I.

This classification is admittedly arbitrary and does not by any means encompass the entire field of chemoprophylaxis. For example, the suppression of overt malarial infection by the administration of antimalarial agents during the incubation period certainly is one of the important milestones in modern chemotherapy, but is beyond the scope of this discussion. Similarly, deployment of antibiotics to eradicate carrier states in order to prevent spread of infection will not be covered in this review. Finally, it should be emphasized that this analysis is concerned only with antibiotics as prophylactic agents and no attempt is made to evaluate their therapeutic efficacy.

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II. The use of antibiotics to prevent infections by specific pathogens

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CERTAIN observations in man have shown clearly that microbes are not eliminated when specific drugs are given during the incubation period and that active illness occurs on cessation of therapy. In spite of the therapeutic efficacy of antibiotics, their administration during the early active stages of certain illnesses fails to prevent recrudescence. The factors responsible for this seeming paradox are not clearly understood and the time relationships between the institution of specific treatment during the early stages of infection and the tendency to relapse are not defined.

SUPPRESSION OF OVERT DISEASE FOLLOWING DEFINITE INFECTION

The present discussion will deal with the effect of antibiotics given during the incubation period or during the early stages of illness in patients with scrub typhus fever, Q fever, tularemia, and typhoid fever. These diseases are of considerable interest since they represent a group characterized by intracellular parasitism about which basic information concerning mechanisms of immunity is incomplete. Clinically these illnesses are often characterized by relapse; the cause for this phenomenon and methods aimed at its prevention are not clearly understood, but some information pertaining to these relationships in man is available.

Scrub typhus (Tsutsugamushi disease). The patient with scrub typhus responds dramatically to treatment with chloramphenicol or the tetracycline antibiotics.[1] Defervescence occurs in an average of 30 hours, and patients initially seriously ill and toxic become alert and afebrile in a very short time.

The antibiotic does not eradicate the causative rickettsia from its intracellular environment but merely suppresses multiplication through its rickettsiostatic properties. Ultimate cure is dependent upon the development of the patient's own immune defenses. The immune state develops about two weeks after the initial antigenic stimulus and if the antigenic mass is diminished by antibiotic suppression, complete resistance to the infection may not develop and relapse occurs. Presumably the antigenic stimulus by *Rickettsia orientalis* is less than with other rickettsiae, and patients given anti-

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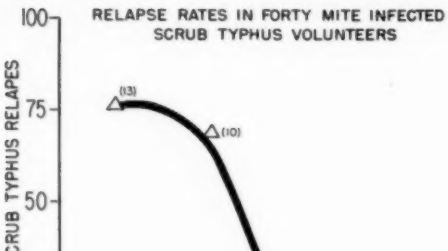


Fig. 1. Effect of time of treatment on relapse rate in scrub typhus. (From Ley, H. L., Jr., and Smadel, J. E.: Antibiotics & Chemother. 4: 795, 1954).

biotics early in the first week of scrub typhus experience recrudescence. Under natural conditions patients with scrub typhus treated prior to the fourth day of disease relapsed.[2] Moreover, Smadel and his associates[1] showed that relapses were quite common following short-term antibiotic treatment given on the third day of disease or before. There were fewer relapses when treatment was delayed until the fifth day of disease, and virtually no relapses in patients first treated on the seventh day of disease or later (Fig. 1).

All patients with such relapses responded well to a second course of therapy with no indication that the rickettsiae developed resistance to the therapeutic agent. Generally, the peak of the Proteus OX-K antibody titer was observed on about the twentieth day of disease irrespective of whether antibiotic therapy was given. The maximum titers for the treated groups however, were lower than those of the control patients.

Attempts were made to prevent the appearance of clinical scrub typhus by the intermittent administration of antibiotics. In these studies, the intradermal inoculation of approximately 60 M.U. minimal infectious doses of *R. orientalis* (Karp strain) in human volunteers resulted in a clinical illness typical of scrub typhus after an incubation period of 10 to 12 days.[3] Clinical disease thus induced was suppressed below clinical levels when 3.0 Gm. of chloramphenicol by mouth was given prophylactically on the seventh day after inoculation and continued at 4-day intervals for three or more occasions. Suppression was not complete and rickettsemia occurred in most instances late in the treatment interval period. In volunteers who received 5 and 6 prophylactic doses clinical suppression resulted and overt disease did not develop. However, a 2.0 Gm. dose of chloramphenicol begun on the seventh day after inoculation of viable rickettsia and repeated at intervals of 4 days for at least three occasions failed to prevent the development of active manifestations of scrub typhus. Typhus fever developed during the course of prophylaxis at this lower dose level.

Thus it appeared that a considerable antigenic stimulus was required over an appreciable period to induce immunity. If the dosage of the drug given for prophylaxis was too small or if the duration of its administration was too short, suppression was inadequate and clinical illness resulted.[3]

Based upon the previous observations, predictions could be made that the administration of a *daily* chemoprophylactic dose of antibiotic initiated on the first day of infection (not first day of clinical disease) and continued for 4 weeks would fail to prevent clinical illness but merely prolong the interval of its development.[3] An additional clue came from an earlier study which showed that continuous daily antibiotic prophylaxis during a 9-day period of field exposure and for 2 weeks thereafter merely suppressed disease during the administration of chloramphenicol and for a short time thereafter.[2]

A study of 6 volunteers settled this crucial point. Beginning on the day of infection with viable rickettsiae, each subject received 1.0 Gm. of chloramphenicol daily for 23 days. Each remained entirely asymptomatic

until about 5 days after the last dose. Five days after chloramphenicol was stopped (thirty-second day after inoculation of *R. orientalis*) the initial evidence of clinical scrub typhus infection appeared in 5 of 6 members of this group. These ultimately developed all of the typical clinical manifestations. One subject failed to develop overt signs of typhus fever at any time. In this group the serologic response was delayed and only lower titers developed. Observations in the control group were typical of the clinical and serologic responses seen in treated, febrile patients with scrub typhus.

This unique experience, accumulated over several years, demonstrated that the absence of relapse following a period of therapy or chemoprophylaxis was an indication that immunity had developed in the individual. In general, development of Proteus OX-K antibodies correlated well with the development of the immune state in naturally infected patients. The correlation was not absolute, however, even under natural circumstances, and broke down almost completely when immunization was carried out in conjunction with chemoprophylaxis.

Q fever. Q fever, one of the benign rickettsioses, is caused by *Rickettsia burneti*. Unlike the other rickettsial diseases there is no rash. The disease is present throughout the temperate and tropical areas of the world and the available epidemiologic data suggest that the major route of infection for man is by inhalation of infected dusts, by handling infected materials, or by drinking milk contaminated with the causative organism.[4]

The disease is a systemic disorder and not solely a pneumonic infection. There may be wide fluctuations in temperature ranging from 101° to 104° F. The entire febrile course usually ranges from 3 to 6 days. Respiratory and gastrointestinal symptoms are not conspicuous in the early stage. Headache and fever predominate. Roentgen findings indistinguishable from primary atypical pneumonia are present usually by the third or fourth day of disease, first as patchy areas of consolidation involving a portion of one lobe followed by development of a homogenous ground-glass appearance. In a series of patients who acquired the infection by the respiratory route under artificially induced conditions, roentgen evidence of pneumonitis was noted in one third to one half.[5] In this study the development of pneumonitis was unrelated to the size of the infecting dose. Complications are rare. Coincidentally with defervescence, the appetite returns and convalescence progresses slowly. The disease may be protracted in approximately 20 per cent of cases with fever persisting for 4 weeks or longer. Occasionally relapse occurs, particularly in patients treated with antibiotics during the first several days of disease. The prognosis is excellent and very few deaths have been recorded.

Tigertt and his associates[5] studied groups of young adult male volunteers who were exposed to an aerosol containing viable *R. burneti*. The incubation period of the first group was 17 days and larger infectious doses resulted in progressive shortening (Fig. 2). Twenty-nine volunteers developed clinical signs comparable to those of Q fever acquired under natural conditions. Oxytetracycline therapy was initiated within 24 hours after the onset of persistent fever. Symptoms ceased within 24 to 48 hours. A 3.0 Gm. loading dose of the antibiotic was followed by 0.75 Gm. given every 6 hours for a total dose averaging 20 Gm. over a 5 to 6 day period. In no instance did a clinical relapse develop in this group, a fact which showed that the temporal relationships with respect to dose and time of therapy differ in patients with Q fever and scrub typhus.

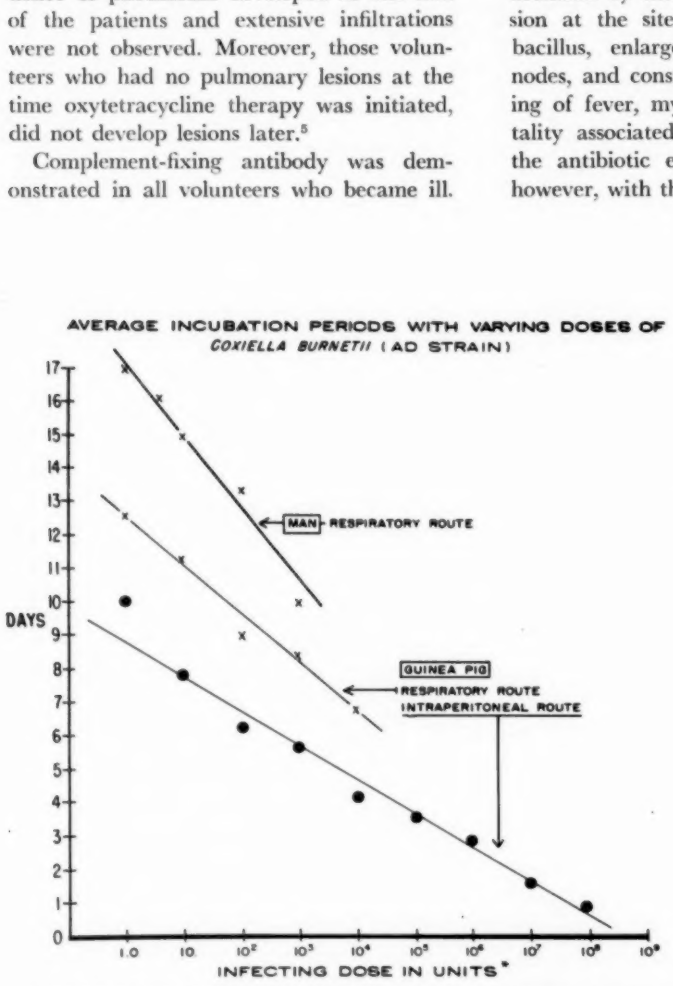
In comparable groups of volunteers prophylactic administration of oxytetracycline was initiated late in the incubation period following the same regimen cited above. Clinical disease was prevented in all instances. However, in a group of men placed on the same prophylactic schedule within 24 hours after exposure to a small dose of *R. burneti*, 4 of 5 developed disease. The incubation period was 8 to 10 days longer

than that of the controls. In this instance the findings in Q fever resembled the situation in scrub typhus. It should be recalled that clinical disease in the group with scrub typhus developed in spite of drug treatment for 28 days given initially on the first day of infection.

There was the usual clinical response to additional oxytetracycline treatment. The active manifestations of Q fever subsided rapidly and there were no instances suggestive of drug resistance. Roentgen evidence of pneumonia developed in one half of the patients and extensive infiltrations were not observed. Moreover, those volunteers who had no pulmonary lesions at the time oxytetracycline therapy was initiated, did not develop lesions later.[5]

Complement-fixing antibody was demonstrated in all volunteers who became ill. The antibody was present within 10 to 2) days after the onset of clinical illness. I those individuals who received oxytetracycline late in the incubation period, the was a delay in the development of specif antibody. This finding is similar to the serologic pattern observed in patients with scrub typhus who were treated early in the course of clinical illness.

Tularemia. Ulceroglandular tularemia is the most common type of clinical disease caused by *Pasteurella tularensis.* It is characterized by the formation of a primary lesion at the site of entry of the causative bacillus, enlargement of regional lymph nodes, and constitutional symptoms consisting of fever, myalgia, and headache. Mortality associated with this disease prior to the antibiotic era was about 5 per cent; however, with the advent of modern chemo-



*One unit is that quantity of *C. Burneti* producing fever in 50 per cent of exposed subjects.

Fig. 2. (From Tigertt, W. D., and Benenson, A. S.: Tr. A. Am. Physicians 69: 99, 1956.)

therapy, death rarely occurred and morbidity was reduced markedly.[6]

Formerly, relapse in tularemia was relatively uncommon, especially when specific antibiotics were administered on the twelfth day of disease or later.[7] In Keefer's series of 67 patients treated with streptomycin there were 2 relapses. However, as antibiotics and particularly those of the broad-spectrum type were administered earlier in the clinical course, i.e., during the first week of illness, recrudescence was noted.[8] In a small series of 7 patients with tularemia treated with chloramphenicol during the first week of illness, 3 relapsed.[8] Each patient responded to re-treatment with the same antibiotic. This has been the experience of others.

In 35 volunteers the ulceroglandular form of tularemia was established by the intracutaneous inoculation of from 400 to 10,000 M.U. $L.D._{50}$ doses of the Rector strain of *P. tularensis*.[6] In untreated control subjects the inoculation was followed in 24 to 48 hours by the appearance of a reddish papule. This subsequently enlarged to a diameter of 1 to 2 cm. and became tender, indurated, and vesiculated. By the third postinoculation day, mild constitutional symptoms of malaise and headache heralded the onset of fever. Moderately enlarged regional axillary lymph nodes were palpable and tender; epitrochlear nodes were rarely present. At this time *P. tularensis* was readily recovered from the primary lesion. In control patients the disease was promptly halted at this point by the administration of antibiotics (Fig. 3).

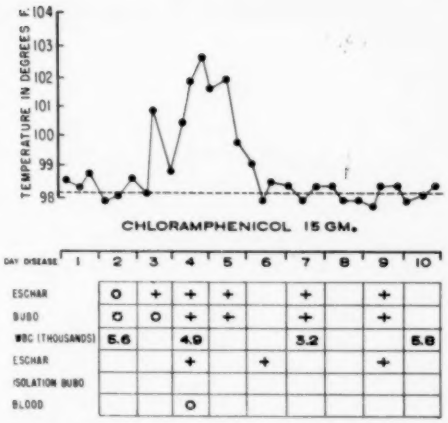


Fig. 3. Tularemia. Course of illness in a control patient who recovered rapidly following the administration of chloramphenicol beginning on the second day of disease. (From McCrumb, F. R., Jr., Snyder, M. J., and Woodward, T. E.: Tr. A. Am. Physicians 70: 77, 1957.)

Seventeen patients received antibiotics one hour after the inoculation of viable organisms. All patients in the prophylactic group received either streptomycin or chloramphenicol for 5 days in amounts of 2.0 and 3.0 Gm. daily, respectively (Table I). Of these, 11 failed to develop any evidence of disease. The control patients received antibiotics within 36 hours of the onset of constitutional symptoms, usually on the fourth postinoculation day.

Clinical manifestations of disease were completely suppressed in 9 of 10 volunteers treated prophylactically with streptomycin; indeed, there was not even a discernible reaction at the site of inoculation. Overt disease developed on cessation of prophylaxis in one subject, a 200 pound man who received relatively small amounts of streptomycin. *P. tularensis* was not isolated from the lesions although agglutinins developed coincidentally with this episode.

In marked contrast to these results was the failure of chloramphenicol to prevent the proliferation of *P. tularensis* after 5 days of prophylactic therapy consisting of 3.0 Gm. daily. Thus, 5 of the 7 volunteers given chloramphenicol prophylactically developed ulceroglandular tularemia following cessation of therapy. The antibiotic succeeded only in prolonging the incubation period. Following a quiescent period of chemoprophylaxis, during which time local lesions were not discernible, the eschar and regional adenopathy evolved as in control patients. All responded satisfactorily to a second course of chloramphenicol or treatment with streptomycin.

Among the controls, 2 received chloramphenicol. Each experienced a febrile relapse. Four other control patients were

Table I. Chemoprophylaxis of experimental tularemia in man*

Therapy group	*Duration (days)*	*Total dose (Gm.)*	*No. of patients*	*Manifest disease*	
				No.	*%*
Streptomycin	5	3	2	1	
	5	10	8	0	
			–	–	
			10	1	10
Chloramphenicol	5	11	2	2	
	5	15	5	3	
			–	–	
			7	5	70
Controls			6	6	100

*From McCrumb, F. R., Jr., Snyder, M. J., and Woodward, T. E.: Tr A. Am. Physicians 70: 77, 1957.

treated with streptomycin and did not relapse in spite of the fact that *P. tularensis* was isolated from eschars as late as 23 days after treatment was instituted.

Without exception, antibody capable of agglutinating *P. tularensis* appeared in the serum of patients who developed clinically manifest disease. Serum agglutinins ranged in titer from 1:40 to 1:2,580 and usually made their appearance during the third or fourth postinoculation week. Conversely, patients in whom infection was fully suppressed failed to develop measurable agglutinating antibody.

Obviously streptomycin was more efficient than chloramphenicol in rendering body tissues free of *P. tularensis*. Whether this suppression is absolute or relative may be a function of the extent to which bacterial proliferation has proceeded prior to the institution of streptomycin therapy. Chloramphenicol seemed incapable of eradicating even small numbers of *P. tularensis* from the nonimmune host.

It is to be emphasized that treatment of patients who have had tularemia for a week or more is usually not attended by relapse whether streptomycin or broad-spectrum antibiotics are given.

Plague. Closely related to tularemia bacteriologically, plague presents a greater public health problem in many parts of the world. Prophylaxis against plague has not been studied as thoroughly as against tularemia, but according to one author[9] overt infection can be prevented by the administration of 3.0 Gm. of sulfadiazine daily for 3 to 7 days. Prophylaxis is said to be particularly effective in protecting contacts of patients with pneumonic plague as well as those bitten by infected fleas or accidentally inoculated with *Pasteurella pestis* in the laboratory. Although highly effective therapeutically, streptomycin is not recommended for mass prophylaxis because the drug must be given parenterally; streptomycin-resistant organisms have also been reported. The tetracyclines may well turn out to be the most potent agents in the chemoprophylaxis of *P. pestis*, but have not received extensive clinical trial.

Typhoid fever. Typhoid fever is one of mankind's major plagues for which there is no absolute control measure. Recrudescence signified by a return of toxic manifestations and typhoidal bacteremia varies in untreated patients from 5 to 15 per cent. A recent review of more than 400 patients treated with chloramphenicol by various investigators[10] indicated an over-all relapse rate of 18.3 per cent. The incidence of relapse observed by most investigators has been essentially similar, approximately 20 per cent when drug regimens for 10 days or less were employed. In most reported series the mean day of disease on which therapy was begun was the fifteenth day, and the duration of therapy was 14 days. Relapse usually occurred about 15 days after cessation of antibiotic therapy, or during the sixth week of disease. In one series of 122 children with typhoid fever, there was a relapse rate of 13 per cent.[11] The author was impressed by the relationship between relapse and the stage of disease at which chloramphenicol treatment was initiated, i.e., the per cent of relapse with respect to beginning treatment during the first, second, and third weeks of illness was 40, 14, and 5 per cent, respectively. In another series of 272 patients[12] for whom reliable data were available, the relapse rate

for those treated in the first, second, and third weeks of illness was 36, 25.5, and 19.7 per cent, respectively. In contrast, in a series of 200 cases, relapse rates of 16.7, 25.5, and 37.5 per cent were reported when treatment was instituted during the first, second, and third weeks, respectively.[13] The relationship between early treatment and incidence of relapse is unsettled, although experience suggests that patients treated early tend to relapse more often.

Although corticosteroids may provoke a precipitous drop in temperature to normal or subnormal levels and exert an ameliorating effect on typhoidal toxemia, their routine use is not advised. Moreover, our recent experience suggests that patients given cortisone during the very early stages of typhoid fever experience a higher incidence of relapse. The point is not established.

Since chloramphenicol is primarily bacteriostatic for *Salmonella typhosa,* it would not be expected to eradicate typhoidal infection if given during the incubation period but would merely suppress the active clinical signs and prolong the incubation period.

Bruceliosis. There are no reliable data pertaining to the effect of antibiotics when given during the incubation period or developmental stages of brucellosis.[14] However, Spink feels that adequate treatment of patients with brucellosis early in the course of illness is very effective and is not attended by a higher incidence of relapse than when specific drugs are given later.[14]

PREVENTION OF DISEASE FOLLOWING POTENTIAL INFECTION

In contrast to the intracellular parasites described in the previous section, antimicrobials directed at the meningococcus, hemolytic streptococcus, gonococcus, Shigella species, and occasionally the staphylococcus, *early* after exposure will in most instances prevent entirely the appearance of clinical disease. Successful antibiotic prophylaxis probably depends on the ability of the drug to penetrate the tissues in sufficient concentration to prevent colonization by the parasite. An alternative explanation is that immune mechanisms play a lesser role in the body's defenses against these microorganisms than is the case in the rickettsioses, tularemia, and typhoid. Thus, if antibody is not essential to the host's defense reaction against the pathogen, eradication of the organism early in the incubation period might be expected to result in complete prevention of symptomatic disease.

Meningococcal infections. Prophylactic antibiotics have been highly effective in terminating epidemics of meningitis. This was particularly evident in military personnel in World War II. In one study performed in an Army Camp,[15] 8,000 men with a meningococcal carrier rate of 36 per cent were treated with 3.0 Gm. of sulfadiazine for 3 days; 9,300 men with a carrier rate of 38 per cent served as controls. Twenty-three of the men in the control group developed meningococcal meningitis, while not a single case was seen in the treated group. Furthermore, the carrier rate decreased to 8 per cent among the men who had received prophylaxis while it rose to 51 per cent in the untreated group. Cheever[16] also noted that administration of 0.5 to 1.0 Gm. of sulfadiazine during a 7-week training period markedly reduced the attack rate of meningococcal meningitis.

In a nonepidemic setting, we have administered 2.0 to 4.0 Gm. of an easily absorbed sulfonamide to all close contacts of patients with meningococcemia or meningitis. While the risk of infection is undoubtedly very small and prophylaxis may not be necessary, the potential hazard of these infections is sufficiently great to justify this practice. No toxic reactions have been noted when sulfonamides were given in this small dosage.

Infections by enteric pathogens. *Shigellosis.* In 1943 Scott[17] reported the arrest of a rapidly progressive epidemic of *Shigella sonnei* dysentery by the prophylactic use of sulfaguanidine. Similar results were reported by others, employing both absorbable and nonabsorbable sulfonamides.[18, 19] All of these

encouraging results were reported in acute epidemics and involved only short courses of prophylactic chemotherapy. Higgins evaluated the effectiveness of long-term daily prophylaxis against Shigella dysentery.[20] Under these conditions, the attack rate in children receiving sulfadiazine was as high as in the controls. Dihydrostreptomycin and oxytetracycline reduced the attack rate by about 50 per cent, but were by no means capable of preventing episodes of acute Shigella dysentery. No strains of Shigella emerged resistant to sulfadiazine but the number of strains resistant to dihydrostreptomycin was double that in the controls. Resistance to oxytetracycline was even more flagrant, and there were four times as many resistant strains in the treatment group as in the controls.

Other diarrheal diseases. The problem of prophylaxis in shigellosis is closely related to the use of antimicrobials by individuals who are traveling in endemic areas of enteric infection. It has been shown that the vast majority of diarrheal diseases in travelers are not due to Shigella, Salmonella, pathogenic *E. coli*, and *Endamoeba histolytica*.[21] Whatever the cause of diarrheal disease among travelers, antimicrobial prophylaxis was notoriously ineffective in averting this common disorder.[22] Of 1,265 United States residents flying into Mexico, 444 took medication—mostly some form of an ambecide—to prevent diarrhea, and 53 per cent became ill. In contrast, only 15 per cent of 821 tourists who took no drugs developed diarrhea. In a prospective double-blind study, American summer students in Mexico City were given a halogenated quinoline, neomycin, or placebo. The antiamebic drug exerted no effect whatsoever; neomycin afforded a slight degree of protection. More careful bacteriologic data are needed to assess the significance of these findings. Suffice it to say, the available data indicating that amebiasis can be prevented by administration of iodides or arsenicals consist of small, poorly controlled studies[23, 24] which require confirmation.

Pathogenic E. coli. Certain serologically identifiable types of *E. coli* are now generally accepted as a cause of gastroenteritis in infants. Usually these strains are isolated in nurseries from babies presenting with diarrhea. It should be pointed out, however, that a significant number of asymptomatic infants excrete these organisms in the stool, and that 1 to 2 per cent of the adult population are fecal carriers.[25] Despite the fact that these organisms may spread from infant to infant with ease, the relatively low incidence of symptomatic diarrhea following infection and the difficulties inherent in identifying pathogenic strains make routine prophylaxis of *E. coli* carriers impracticable.

Wheeler[26] examined the effect of antimicrobial prophylaxis in an epidemic of infantile diarrhea associated with *E. coli* 0-111 B4. He found both penicillin and sulfadiazine incapable of preventing further infection. Administration of chloramphenicol also failed to halt the spread of diarrhea and a number of chloramphenicol-resistant strains appeared. All cultures became negative and no further cases developed after therapy with neomycin 50 mg. per kilogram was instituted. It appears that neomycin is the drug of choice in the prophylaxis of gastroenteritis with pathogenic *E. coli*. This is in agreement with in vitro studies in our laboratory which also indicate that kanamycin and colistin (an analogue of polymyxin B) given orally should be effective.[27] The last-mentioned eliminated pathogenic *E. coli* from the gastrointestinal tracts of 10 of 11 children.[28]

Gonococcal infections. It has been well documented that gonorrhea can be prevented by small doses of oral penicillin taken shortly after sexual contact. The administration of 100,000 to 250,000 units of oral penicillin to naval personnel returning from shore leave reduced the incidence of infection to 20 per cent of that in the control group.[29] With the exception of one questionable case, gonorrhea was prevented in 670 "liberties" protected with penicillin while 6 cases occurred in 1,273 unprotected liberties. These data suggest that the time interval between exposure and initiation of

prophylaxis is important, and that significant delays between contact and administration of prophylaxis will vitiate the protective effect of penicillin. Sulfonamide-resistant strains of gonococci are frequent nowadays and this agent should not be used for prophylaxis. It should also be emphasized that penicillin in low dosage, recommended for prophylaxis of gonorrhea, will not protect from syphilis although the symptoms of the primary syphilitic infection may be masked. This is of obvious importance from the public health point of view. While the prevention of syphilis with penicillin is theoretically possible, the amount required would be much larger, making mass prophylaxis impractical.

Instillation of penicillin into the eyes is unequivocally effective in protecting newborn infants from gonococcal ophthalmia. A number of other regimens including ocular lavage with sterile water, sterile saline, 1 per cent silver nitrate, tetracycline, oxytetracycline, and bacitracin have been equally successful.[30] Despite the occurrence of chemical conjunctivitis following its use, Posner prefers the old-fashioned instillation of silver nitrate because of the danger of sensitization to antibiotics or the emergence of drug-resistant strains.[30] Actually, use of penicillin entails a minimal risk and its continued use appears justified.

Staphylococcal infections in newborn infants. Staphylococcal infections of the newborn have gained considerable prominence in recent years and have become an important public health problem. Whether the increased incidence of these infections is a consequence of the widespread use of antibiotics resulting in the emergence of resistant strains, or whether more virulent strains are responsible for these infections is not clear.[31] Suffice it to say, the newborn infant appears to be a highly susceptible host. Staphylococcus in the newborn is usually manifested by pyoderma, breast abscess, pneumonia, empyema, and occasionally sepsis. Frequently, infection does not become evident until after the baby has been discharged from the nursery. The staphylococcus is then carried into the home and siblings and parents are infected with the parasite. All of us have seen families with persistent staphylococcal disease which had been acquired in the hospital months and even years previously.

The factors governing the pathogenesis and epidemiology of staphylococcal infections in nurseries are complex, and the roles of personnel carriers, transmission from infant to infant, as well as the importance of airborne route, bedding, blankets, etc., have not been clearly defined. It has been established that, in the majority of instances, epidemics in nurseries have been caused by a single strain; most often this strain has been lysed by phages 52/42B/80/81[32] or 42B/47C/44A/52.[33] These strains are usually resistant to penicillin, streptomycin, and the tetracyclines but are sensitive to erythromycin, chloramphenicol, novobiocin, kanamycin, bacitracin, and vancomycin. The persistence of these strains in the nurseries despite adoption of stringent aseptic techniques led Shaffer[32] to employ erythromycin in dosage of 44 mg. per kilogram in an attempt to eradicate an epidemic at the Ohio State University Hospital. None of the babies who were given erythromycin during at first 7 days of life developed infections either in the hospital or at home. In contrast, infants whose antistaphylococcal regimen consisted primarily of hexachlorophene baths were kept free of infection while in the hospital but developed staphylococcal disease at home. Erythromycin also markedly reduced the rate of colonization of these infants and only 5 of 71 receiving the drug became staphylococcal carriers, while 24 of 74 taking only hexachlorophene baths were colonized. During a period when all infants were given erythromycin, only one infection occurred. Erythromycin-resistant strains did not appear. Kresky[34] corroborated this salutary experience with erythromycin and was able to control an epidemic of staphylococcal infection in a small nursery. On the other hand, Fekety and co-workers[33] failed to arrest an epidemic with erythromycin, and staphylococcal infections did

not cease until infected personnel were removed from the nursery. Our experience in treating adults also indicates that the carrier state with one of the epidemic strains, particularly phage type 42B/52/80/81, is extremely refractory to treatment with antibiotics. While the organism always disappears during chemotherapy, it tends to return to its habitat several weeks after antibiotics are discontinued.[35] The use of erythromycin to abort epidemic staphylococcal disease in nurseries is certainly acceptable practice but should not replace strict asepsis and removal of infected contacts from the environment.

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III. Prophylaxis of poststreptococcal sequelae and bacterial endocarditis

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PREVENTION OF INITIAL ATTACKS OF RHEUMATIC FEVER

THE appropriate use of effective therapeutic agents for the control of streptococcal infections has made possible the prevention of rheumatic fever and glomerulonephritis. Numerous studies have shown that prompt, adequate treatment of streptococcal pharyngitis will prevent the development of these nonsuppurative complications which would otherwise occur in about 3 to 5 per cent of the exposed population.[1, 2] Although treatment should begin as soon as the infection is discovered, recent work has shown that the promptness of treatment is not crucial. Even if the streptococcal infection has been clinically apparent for as long as 9 days and has elicited an antibody response, rheumatic complications can often be prevented by adequate therapy begun at that time.[3] Thus a time lag of 1 or 2 days will not be harmful in cases of pharyngitis or upper respiratory ailments which do not seem to be streptococcal and for which the physician may wish to withhold therapy until the results of throat culture are obtained.

Despite the effectiveness of these measures, they do not solve the problem of poststreptococcal complications. The difficulty is that many streptococcal infections are never identified because at least half of them do not create symptoms.[1, 4, 5]

These asymptomatic infections will escape recognition and will not be treated because the patient does not seek medical attention. In this way rheumatic fever or glomerulonephritis can develop without any previous clinical warning. For these reasons, the prevention of *first* attacks of rheumatic fever cannot be entirely successful. The rheumatic attack rate can be reduced by providing adequate treatment for those streptococcal infections which can be identified clinically or bacteriologically. To find the asymptomatic infections would require screening and examination techniques which are not currently practical or established on a mass scale.

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Studies of primary prevention of rheumatic fever in civilian groups—chiefly school children—have been difficult to analyze because of the presence of a high percentage of asymptomatic streptococcal carriers. When school populations were examined routinely during the school year,[6, 7] approximately one half of the children were found at various times to harbor beta-hemolytic streptococci without clinical or laboratory manifestations of infection. This occurred regardless of attempts to control carriers by penicillin treatment. Conversely, respiratory symptoms in these children were often not associated with streptococci in the throat or nasopharynx. For these reasons, there is some doubt that satisfactory prevention of rheumatic fever can be achieved as has been reported[8-10] by routine culture of the throats of school children and by treating all whose cultures are positive. The issue is still unsettled. It seems likely that the ultimate solution to this problem will come only with the development of a vaccine. The development of reliable, mass-immunization techniques against streptococcal infections remains a problem for future investigation.

Identification of streptococcal infections. Since so many streptococcal infections are asymptomatic and are detected only by throat culture or antibody tests, it is apparent that the most frequent cause for failure to diagnose the infection is the patient's failure to develop clinical symptoms. In symptomatic patients, the most common cause for failure to recognize the infection is the absence of signs and symptoms of pharyngitis. When pharyngitis is present but does not appear clinically to be streptococcal, failure to culture the throat will allow the organism to remain undetected. Finally, the physician may take a throat culture which contains streptococci but it may not be properly processed or its laboratory management may not be adequate. Because the use of routine throat cultures has not become a part of standard medical practice, it is possible that the indiscriminate use of antibiotics[11] for all upper respiratory ailments may actually be of some advantage since this will provide treatment for certain streptococcal infections which would otherwise be unrecognized. It seems likely that some of the reduction in primary attacks of rheumatic fever is attributable to this feature of modern medical care. However, the problem of unrecognizable streptococcal infections obviously will not be solved by the indiscriminate use of antibiotics for three reasons: In the first place, physicians who engage in this practice often also fail to employ a dosage which is adequate for eradication of streptococci. Second, the risk of complications due to antibiotic therapy may outweigh that of untreated streptococcal infection. Finally, medical care based on this philosophy will still fail to reach those infections which are completely asymptomatic.

These considerations illustrate the difficulties of making a purely clinical diagnosis of streptococcal infection and emphasize the need for appropriate laboratory assistance. The identification of streptococci rests upon their direct demonstration. This can be done either by growing the organism in culture[12] or by reacting it with serum-containing antibody which combines with streptococci to make a combination which is visibly fluorescent.[13] The fluorescent antibody techniques have the advantage of simplicity and rapidity but have not yet come into general use. In addition, streptococci not belonging to Group A occasionally give rise to falsely positive reactions. For greatest accuracy the organism should be grown in culture. When beta-hemolytic streptococci appear, they should be tested with antisera to demonstrate that they belong to the pathogenic Group A. Growth on culture requires that the original throat swab be placed directly on or in an appropriate medium. If it cannot be streaked immediately on a blood agar plate, the swab should be kept from drying by keeping it in broth. Pike's enriched broth[14] has been used to advantage for this purpose because it prevents overgrowth of other organisms. When the swab is plated directly, ordinary sheep blood-agar plates are quite satisfac-

tory. They may also be used for streaking a loopful of the swab-in-broth. Identification is often improved when a few deep colonies are implanted by making stabs into the agar. When broth is used, some workers prefer to make fresh pour plates using melted agar.[7] Pathogenic streptococci produce clear zones of hemolysis (beta-hemolysis) and must be differentiated from nonpathogens which produce no hemolysis or a partial green (alpha) form. Hemolytic staphylococci and gram-negative cocci may also produce clear zones of hemolysis on blood-agar plates but can be easily identified by their gross and microscopic morphologic characteristics. The methods for streptococcal culturing and identification of streptococci have been described in detail by Wannamaker[12] and others.[15, 16] It appears likely that direct culture techniques will continue to be used for the foreseeable future. These techniques may eventually be replaced by fluorescent antibody methods or other tests in which the organism is identified directly.

Prophylaxis of streptococcal infections in patients who have had rheumatic fever. As noted previously, not all streptococcal infections are clinically recognizable and many will escape treatment. In order to prevent recurrences of rheumatic fever, subjects whose first attack signifies their susceptibility to recurrences cannot rely upon the identification of these infections and must attempt to prevent them. This is the rationale for the use of prolonged, continuous antistreptococcal prophylaxis in these patients. Unless replaced by intervening courses of other antibiotics, prophylaxis must be given continuously or repetitively to avoid the development of streptococcal infections with their associated hazard of recrudescent rheumatic activity. Control of these infections by continuous prophylaxis or by repeated therapeutic courses given intermittently has been almost universally accepted.[17] However, one recent report[18] has rejected this approach and claims equally good results in preventing rheumatic fever by avoiding prophylaxis and treating streptococcal infections as they appear. The validity of this method cannot be determined from the available data.[19]

Studies of long-term prophylaxis differ considerably from those in which drugs are used in short-term acute projects. If the results of these long-term studies are to be valid, their design must adhere to certain scientific standards:

1. Susceptibility of the patients must be clearly established. (Thus in prophylaxis against rheumatic fever, the diagnosis of rheumatic fever must be unequivocal in all patients.)

2. The number of patients must be large enough for statistical analysis. The groups to be compared should be studied simultaneously, not sequentially, and they must be comparable in regard to certain crucial clinical parameters.

3. The patients must be examined frequently and vigorous attempts must be made to obtain studies from patients who fail their appointments.

4. Any antibiotic therapy other than the planned regimen should be avoided because it would affect the bacterial flora and might alter the results of prophylaxis. This is particularly important when a major purpose of prophylaxis is the prevention of *subclinical* infections.

5. In order to determine whether asymptomatic streptococcal infections have occurred, it is necessary to perform frequent antibody tests as well as throat cultures. Antibody levels should be determined sequentially to measure changes in titer rather than absolute levels and should include several different antibody tests (antistreptolysin, antihyaluronidase, and antistreptokinase) to avoid missing those infections which will result in elevation of only one of these antibody titers.

6. When the results are analyzed, it is important to separate the effects of the medication per se from those of the regimen in which it is employed. Thus, prophylactic drugs taken by mouth are often forgotten, misplaced, or lost, and the results of failure to take the medication should be distinguished from failure of the medication itself.

Choice of prophylactic agent. Of the many available studies of prophylaxis against recurrent attacks of rheumatic fever, only one large-scale, civilian study has carefully conformed to all the above scientific requirements.[20] The data accumulated at Irvington House[20] show that monthly repository injections of benzathine penicillin prevent rheumatic recurrences better than oral preparations of sulfadiazine or penicillin, even when the oral preparations are taken faithfully in dosage as high as 200,000 units per day. Repository penicillin injections, however, may not always be desirable because of the marked pain and discomfort which they provoke in about 10 per cent of patients and because of their potentiality for sensitization. Hypersensitivity reactions are rarely observed in the age group consisting primarily of children and adolescents but later may become a prominent deterrent to use of the drug in older patients.[21] Of the two oral preparations, sulfadiazine, 1.0 Gm. per day, was at least as effective as either 200,000 or 400,000 units of penicillin per day. This observation is well documented and contradicts many unsupported claims for the superiority of oral penicillin as a prophylactic agent. Although oral penicillin may be bactericidal, it is unlikely that the doses employed for prophylaxis are of sufficient magnitude to achieve a bactericidal effect. A regimen alternative to that of taking oral penicillin daily consists of a course of penicillin designed to *eradicate* streptococci at monthly intervals. Such a program has not been validated statistically but the results to date have been quite favorable.[22] Certainly the rationale of this regimen is reasonable. The latent interval between the attack of streptococcal pharyngitis and the onset of rheumatic fever is generally assumed to be about 2 weeks, and certainly less than 35 days. However, pharyngitis may be the first clinical manifestation of an infection which had been present for an unknown length of time before it became symptomatic. Thus the latent period between entrance of the organisms into the throat and the development of rheumatic fever may actually be much longer than the interval measured from the onset of clinical pharyngitis. If the infection is present for more than 30 days before development of rheumatic fever, repetitive monthly eradication of streptococci might prevent rheumatic recurrences more effectively than a prophylactic oral agent which does not reach therapeutic levels.

In this regard, it is important to recall that monthly injections of benzathine penicillin are sufficiently potent to eradicate streptococci as well as provide a persistent blood level. The effectiveness of these injections in antirheumatism prophylaxis has usually been attributed to their ability to persist in the blood but may conceivably be due to the effects of the higher streptococcicidal levels which exist for the first few days after administration. For these reasons, the usefulness of repetitive monthly therapeutic courses of oral penicillin as a prophylactic regimen will need further investigation.

Alternative agents are available for prophylaxis. Erythromycin has been employed with contradictory results[23, 24] and chlortetracycline has also been used.[25] The rationale for these preparations is that they avoid the problem of penicillin hypersensitivity and presumably are more effective than the bacteriostatic sulfonamides. The reluctance to use sulfonamides in place of penicillin apparently stems from the fear of allergic or toxic reactions, coupled with the realization that sulfonamides do not eradicate streptococci. In point of fact, however, the data show clearly that sulfadiazine is an effective prophylactic agent and is associated with a negligible incidence of side reactions. Tetracycline and erythromycin have not been compared with sulfadiazine under controlled conditions and the relative efficacy of these agents has not been determined. Furthermore, the expense of these drugs restricts their use in long-term prophylaxis. A long-acting oral sulfonamide preparation, sulfamethoxypyridazine, offers the advantage that it need not be taken daily and may provide effective oral prophylaxis

when taken once weekly.[26, 27] Its effectiveness over a prolonged period and the incidence of reactions to it remain to be established.

Choice of patients for prophylaxis. In choosing patients for prophylaxis, a history of rheumatic fever must be clearly established. The diagnosis of rheumatic fever appeared erroneous in 12 per cent of a series of patients referred to a special treatment center[28] and the incidence of these errors may even be higher in some of the state-wide programs which do not attempt to confirm the diagnosis in each patient.[29] It is imperative that the original diagnosis be correct before assigning a patient to a prolonged, perhaps lifetime, regimen of continuous prophylaxis which may otherwise be needless and potentially harmful. It has been suggested that demonstration of a recent streptococcal infection be made a prerequisite to the diagnosis of most cases of acute rheumatic fever. This problem requires further evaluation. Obviously, every effort should be made to establish the diagnosis by bacteriologic or immunologic means.

Duration of prophylaxis. The recurrence rate of rheumatic fever is highest in the first 3 years after attack, remains relatively high for the next 2 years, and diminishes thereafter with the passage of time.[30-32] It is, therefore, necessary to maintain prophylaxis for at least 3 years, and preferably 5 years after the attack. The length of time that prophylaxis should be continued thereafter has not been determined and current recommendations are that it be maintained "indefinitely." The accumulation of additional information in the next few years may modify this recommendation. It has been shown, for example, that the attack rate of streptococcal infections diminishes after patients have passed their sixteenth birthday. Similarly, it is now known that the recurrence rate of rheumatic fever per streptococcal infection is reduced as patients grow older. These studies of rheumatic recurrences[33] suggest that repeated attacks are associated with further cardiac damage only in patients who had valvular involvement with their initial attack and that those whose hearts were spared during the first episodes remained free of valvular involvement during subsequent attacks. Confirmation of these results may enable prophylaxis to be discontinued at an earlier time in patients who have not had valvular involvement. The decrease in susceptibility to recurrent attacks beyond adolescence[34] and the relatively benign nature of first attacks occurring in adulthood[35] suggest that prophylaxis in adults need not be maintained as long as in the younger age group. For the present, it seems reasonable to continue prophylaxis for at least 5 years in all patients, to maintain it through the elementary and high school years, and to resume it (if it has been stopped) when the patient becomes particularly susceptible or exposed to streptococcal infections as in pregnancy or military service.

A frequent problem occurs in adults when inactive rheumatic heart disease is discovered de novo or exists as a residue of a remote known attack. Recurrences in adults with heart disease are potentially far more dangerous than in those who have only a history of rheumatic fever without residual heart disease or who had a recent first attack without valvulitis. The choice lies between the use of continuous prophylaxis or a vigorous attempt to identify and treat streptococcal infections as they occur; the former course seems preferable.

Complications of continuous antimicrobial prophylaxis have, in the younger age groups, been remarkably rare. In the Irvington House studies, which now extend over a 7-year period, resistance among microorganisms has not developed, no systemic hypersensitivity reactions to repository penicillin have been observed, and no significant changes in the bacterial flora of the pharynx have been noted. The recurrence rate of rheumatic fever, regardless of the choice of preparation, has been kept sufficiently low that there appears to be no need for the administration of prophylaxis to the family of rheumatic patients.

Prophylaxis of acute hemorrhagic glomerulonephritis. Next to rheumatic fever, the

most serious sequela of streptococcal infections is acute glomerulonephritis. Therefore, early recognition and treatment of these infections are mandatory if this complication is to be avoided. Unfortunately, in a number of instances, acute glomerulonephritis also follows asymptomatic streptococcal infection. However, in contrast to rheumatic fever, the patient who has recovered from an attack of acute nephritis is not susceptible to recurrences of the disease when he contracts an infection with hemolytic streptococci. The explanation for this phenomenon is that in most instances acute glomerulonephritis follows infection by only certain types of Group A streptococci, notably Types 4 and 12. Once a patient has been infected by these strains he acquires type-specific immunity and recurrences will not take place. For this reason, prophylaxis against streptococcal infection contributes little to the management of a patient who has had acute glomerulonephritis and the only way in which glomerulonephritis can be prevented is by prompt and adequate treatment of the primary streptococcal infection. It is equally important to treat all members of the family or group with which the patient is in close contact with penicillin since the incidence of nephritis is very high following colonization with certain nephritogenic strains of streptococci.

PROPHYLAXIS OF SUBACUTE BACTERIAL ENDOCARDITIS

In essence, the prevention of subacute bacterial endocarditis (S.B.E.) is synonymous with the prevention of bacteremia. It seems reasonable, therefore, to examine first the portals of entry of the microorganisms causing S.B.E., to correlate this information with the incidence of bacteremia following disease or surgical manipulations in these locations, and then to evaluate the effect of antibiotics in preventing bacteremia and S.B.E.

The most common paths of entry for microorganisms in documented cases of S.B.E. have been[36]: (1) the mouth, gums, and teeth; (2) the upper respiratory tract, particularly the tonsils and sinuses; (3) the urinary tract in males; and (4) the genital tract in females. In addition, since the advent of cardiac surgery, direct entry into the blood stream has become a relatively common path of infection.

Subacute bacterial endocarditis affects patients with rheumatic heart disease in 90 per cent of the cases; congenital lesions, predominantly bicuspid aortic valves, patent ductus arteriosus, interventricular septal defect, coarctation of the aorta, and pulmonic stenosis, account for 5 per cent of cases; and in the remainder normal valves are involved. Curiously, atrial septal defects and syphilitic aortitis rarely serve as a source for implantation of bacteria. The causative organisms consist of alpha streptococci in the majority of instances; other types of nonhemolytic streptococci, enterococci, and hemolytic and nonhemolytic staphylococci account for most of the remainder. Occasionally gram-negative bacilli, Neisseria, pneumococci, and Group A streptococci infect the heart valves. It should be emphasized that S.B.E. is only rarely caused by Group A streptococci which are the organisms eliminated by long-term penicillin prophylaxis. Measures, therefore, aimed at the prevention of rheumatic fever, do not prevent the development of S.B.E.

Bacteremia following dental manipulation. Glaser[37] thoroughly reviewed the literature concerned with the incidence of bacteremia following dental extraction. Bacteremia varied from 10 per cent after a single extraction to 80 per cent following extractions of multiple teeth. Pyorrhea and inflamed gums tended to increase the incidence of bacteremia. Blood-stream invasion was not only associated with extractions but any vigorous manipulation of teeth or gums such as chewing paraffin or rock candy was attended by bacteremia. Bacteremia was usually transient and blood cultures obtained 30 minutes after extraction were generally sterile. Penicillin given for 24 hours prior to manipulation of teeth diminished the incidence of bacteremia but by no means eliminated it. This program seemed to be more effective in patients with diseased teeth and gums than in those whose teeth were

normal. The presence of penicillinase in all cultures may have favored the growth of organisms in vitro when, in the absence of penicillinase, their growth might have been inhibited in vivo.

Hirsh[38] administered 600,000 units of penicillin in oil 3 to 4 hours before tooth extraction to 65 patients; an equal number served as controls. Blood cultures were obtained 1, 10, and 30 minutes after extraction and the per cent of positive cultures in the treatment group was 20, 15, and 11 per cent, while 34, 22, and 12 per cent of controls had bacteremia. While these figures were not statistically significant, the incidence of bacteremia with alpha streptococci was 34 per cent in the untreated group and 15 per cent among those given penicillin. More importantly, although 4 of 11 patients with rheumatic heart disease had bacteremia after tooth extraction (3 with alpha streptococci, and 1 *Staphylococcus albus*), none developed S.B.E.

These results suggest that the success of prophylaxis did not hinge on prevention of bacteremia but that the antibiotics may have kept the organisms from being implanted on the heart valves. Despite the estimated small risk following single extractions in susceptible patients, it should be remembered that 1 of 4 cases of S.B.E. occurs subsequently to dental work. Therefore, it is recommended that all susceptible patients be given prophylactic chemotherapy according to the following regimen[39]: (1) for 2 days before dental surgery, 250,000 units of oral penicillin, 4 times daily before meals; (2) on the day of dental surgery 600,000 units of crystalline aqueous and 600,000 units of procaine penicillin intramuscularly shortly before extraction; (3) for the 2 days after extraction, 250,000 units of oral penicillin, 4 times daily before meals.

An alternative method is to give 600,000 units of procaine penicillin on the day before, of, and after surgery. On the day of tooth extraction, 600,000 units of crystalline aqueous penicillin should be added shortly before the procedure.

Roth and colleagues[40] demonstrated that bacteremia was abolished in normal patients and patients with heart disease following tooth extraction provided they were given 2 Gm. of chlortetracycline on the day prior to extraction. These results suggest that in patients who are allergic to penicillin, chlortetracycline would serve as an acceptable substitute.

The instillation of antibiotics into tooth sockets or the ingestion of antibiotic troches did little to reduce bacteremia[41] and this form of prophylaxis does not seem to be of particular value.

Bacteremia following tonsillectomy. Blood cultures obtained immediately after surgical removal of tonsils have been positive in 30 to 40 per cent of patients.[42, 43] Rhoads and co-workers[43] found that penicilllin had to be given in large doses over a relatively long time in order to reduce significantly the incidence of bacteremia. For example, 900,000 units of oral penicillin for 5 to 7 days before operation failed to clear the blood stream in 57 per cent of patients. Similarly, procaine penicillin given for only 1 to 2 doses before the operation was incapable of eliminating bacteria from the blood stream in 30 per cent of cases. In contrast, when procaine penicillin in dosage of 600,000 units a day was given intramuscularly for 4 to 10 days, bacteremia was noted in only 6 per cent. Erythromycin and oxytetracycline did not prevent invasion of the blood stream. Prophylaxis was effective in eliminating bacteremia with Group A streptococci but alpha streptococci were reduced by only one third. Of interest was the finding that Group A streptococci were found in 22 per cent of excised tonsils even after prophylaxis was completed. These findings suggest that susceptible patients should be given penicillin by the parenteral route for one week preceding tonsillectomy.

Bacteremia and S.B.E. following urethral manipulation. Bacteremia is a common occurence following urethral catheterization, cystoscopy, transurethral resection, and other surgical procedures involving the lower urinary tract. Scott[44] cites a figure of 0.2 per cent among patients undergoing urethral

instrumentation. Creevy and Feeney[45] report an incidence of bacteremia of 46 per cent in patients subjected to transurethral resection. This figure was unaffected by prophylaxis with penicillin, and penicillin and streptomycin but was reduced by about 50 per cent after administration of sulfisoxazole or broad-spectrum antibiotics. The susceptibility of patients with valvular heart disease to S.B.E. following manipulation of the urinary tract has been documented by Merritt who described 8 cases as a complication of transurethral prostatic resection,[46] and Meneely[47] who described 2 cases following urethral dilatation. When S.B.E. has emanated from the urinary tract, the causative organisms have usually been *Streptococcus faecalis,* enterococcus, and occasionally gram-negative bacilli. In view of this, prophylaxis should consist of: (1) penicillin, 1,200,000 units, intramuscularly for 2 days prior to the day of, on the day of, and 2 days after, operation, and (2) streptomycin, 1 Gm., and one of the tetracyclines, 1 Gm., given over the same period.

Although the efficacy of this program has not been established, the refractoriness of the organisms to antimicrobials once they have become established on the heart valves, would justify this rigorous regimen.

Bacteremia and S.B.E. after parturition. Although it is often stated that bacterial endocarditis may follow delivery in susceptible hosts,[36] there is little objective evidence on which to base these claims. In a recent study, transient bacteremia was found in only 2 of 101 consecutive deliveries.[48] This figure may be considerably higher following dilatation and curettage or septic abortions. While prophylactic antibiotics should certainly be given to susceptible patients undergoing surgery of the genital tract, including dilatation and curettage, the indications for their use in normal, uncomplicated pregnancies are certainly less clear. The regimen should include a broad-spectrum antibiotic coupled with streptomycin.

Antibiotic prophylaxis following cardiac surgery. The monumental advances in cardiac surgery have brought with them a new and definite hazard—bacterial endocarditis at the sites of valvulotomy, repair of congenital defects, and repair of anastomoses.[49-51] This is admittedly a rare complication but is of considerable importance since it results in a mortality of from 20 to 90 per cent.[51] The diagnosis of postcardiotomy S.B.E. requires a high index of suspicion since the classical picture of bacterial endocarditis is usually not apparent and the findings may be limited to tachycardia and persistent fever. Another factor of importance is that the etiological organisms consist predominantly of *Staphylococcus aureus* and gram-negative bacilli such as Achromobacter and Pseudomonas,[49-52] which are notoriously resistant to antibiotics. The last-mentioned species have at times been introduced via pump-oxygenating apparatus. Silk sutures in the myocardium and great vessels have also served as a nidus for implantation of microorganisms.

One of the difficulties is that patients who have acquired bacterial endocarditis after cardiac surgery have almost invariably received prophylactic penicillin and streptomycin before, during, and after operation. Presumably prophylaxis in these patients is aimed at preventing endocarditis with the common flora, specifically streptococci. Other reasons given for the routine use of antibiotics is that they might mitigate pulmonary infections in a poorly ventilated lung and also protect vascular anastomoses from invasion by bacteria. The use of prophylactic antibiotics in patients undergoing cardiac surgery has not been subjected to study, but may be necessary. While chemoprophylaxis has undoubtedly protected from infection by *Streptococcus viridans,* it has not been effective against the extraordinarily resistant flora responsible for these postoperative infections. Furthermore, although in some instances these resistant organisms clearly resided in a nidus introduced during surgery, or were disseminated via a pump oxygenator, the possibility that antibiotic prophylaxis promoted the selection of a resistant flora exists.

Some surgeons have employed chlo-

ramphenicol and erythromycin as prophylactic agents in patients undergoing cardiac surgery in the hope that this would prevent colonization with resistant microorganisms. This practice has, in our experience, not been successful and in the case of staphylococci has resulted in the emergence of organisms sensitive only to vancomycin, novobiocin, and kanamycin.[53]

This problem can be settled only by a controlled study of chemoprophylaxis in patients subjected to operation for congenital or acquired valvular heart disease. To date such a study has not been performed.

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IV. Protection against infection in susceptible individuals

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THE discussion in this final paper of the symposium deals with the role of antibiotics in the "infection-prone" patient. This term has been used to include a "multitude of sins" and has been the modus operandi for the administration of antibiotics under a variety of circumstances from the common cold to acute renal failure. For the sake of clarity, we have divided this discussion into four parts:

1. The use of antibiotics to prevent infection in the premature infant and neonate.
2. Antibiotic prophylaxis in acute, transient aberrations in resistance, as in burns, following operation, or during viral infections.
3. Chemoprophylaxis in chronic disease.
4. The place of antibiotics in patients receiving irradiation, adrenal hormones, or antimetabolites.

Despite the ubiquitous use of antibiotics in these situations, the indications for their administration have not been clearly defined and require re-examination.

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THE USE OF ANTIBIOTICS IN NEWBORN INFANTS

Two groups of neonates are said to be particularly susceptible to infection, namely, those born after prolonged labor, usually after premature rupture of the membranes, and those born prematurely, particularly if their birth weight is less than 1500 grams. While there is no doubt that infant mortality is high in each of these groups,[1] the role of *infection* as a cause of death has not been clearly established. For example, in 121 neonates in whom a cause of death was determined at necropsy, only 14 had clear-cut evidence that infection, in this instance, pneumonia, contributed to death. In the same study, omphalitis was present in 38 per cent of infants following prolonged labor but contributed little to systemic disease or death.[1] The argument that neonatal mortality has dropped from 44 per 1,000 in 1915 to 19 per 1,000 in 1955, because antibiotics were given freely during that year, fails to take into account that there has been a steady decline in infant mortality, most of which occurred prior to the antibiotic era.[2] For example, in 1932, 10 years before the discovery of penicillin, the rate was 32 per 1,000. Similarly, preliminary estimates made

in 1950 that antibiotics had had a favorable effect on neonatal mortality at the Boston Children's and Boston Lying-in Hospitals failed to consider that individual incubators were introduced concomitantly with the decrease in infant mortality.[3] Four years later at the same center only one premature infant in 143, 92 of whom did *not* receive antibiotics, died from infection.[3] On the other hand, some authors report an increased incidence in neonatal infections in premature infants and recommend administration of these agents to babies born after prolonged labor or with premature rupture of membranes,[4-6] and some also administer antimicrobials to the mothers.[7, 8]

Employing the combination of maternal pyrexia and fetal tachycardia as criteria for intrapartum infection, Smith[7] treated 69 mothers with 2.0 Gm. of streptomycin intramuscularly and 2.0 Gm. oxytetracycline by mouth from diagnosis to delivery; an equal number remained untreated. The incidence of maternal pyrexia and fetal mortality was twice as high in the untreated group as in that receiving antimicrobials. Furthermore, 50 per cent of deaths in the control group were attributed to pneumonia, while there was no evidence of this infection among infants of mothers who had been treated.

In another study,[8] half the mothers admitted to an obstetrical unit received penicillin shortly after admission and their offspring were similarly treated. There were 835 mothers and 843 children in the treatment group and 897 mothers with 908 infants in the control group. Each group contained approximately the same number of premature infants but the evidence of prolonged labor was three times as great among mothers given antibiotics. This suggests that the nurses who were responsible for assigning the mother to each study group on an alternate case basis favored mothers with difficult labor by placing them in the antibiotic group. This pitfall, which is inherent in any study which does not employ a strictly double-blind technique, invalidates much of this otherwise well-planned experiment. While the mothers receiving antibiotics had somewhat less fever than controls, mortality was not affected among premature and full-term infants. Three babies developed abscesses while on penicillin, and intrauterine pneumonia was noted in another infant on this drug. Since the data are skewed somewhat in favor of the control group, one might have expected a higher mortality among control infants of mothers with prolonged labor if they had not received antibiotics. In an uncontrolled study,[9] it was shown that the mortality in infants given antibiotics because of premature rupture of the maternal membranes was 2½ times that of untreated controls. This increase in mortality was attributed to the use of chloramphenicol, in doses of about 100 to 150 mg. per kilogram with subsequent development of "gray sickness."[10] Although better studies are needed, the results to date suggest but do not prove that antibiotics given to mothers and infants may favorably affect infant mortality and maternal mortality in cases of prolonged, difficult labor.

When susceptibility to infection and response to chemoprophylaxis are considered for premature infants regardless of duration of labor, the picture is even less clear. Among 100 premature infants given 300,000 units of penicillin daily for 96 hours after birth, the neonatal mortality was 17 per cent with infection contributing to death in one instance.[11] Among the untreated controls, 25 per cent of infants died, with infection (pneumonia 6 times and meningitis once) implicated in 7. On the other hand, the number of infections was the same in both groups, and, if penicillin had any effect, it prevented death from infection but not infection per se. In the majority of both groups, however, death was presumed to be due to atelectasis and not infection.[11] Attempts to correlate the nasopharyngeal flora with mortality among premature infants have not been successful.[3] In Stoppelman's study, antibiotics tended to decrease streptococci but had no effect on the emergence of staphylococci. Pure cultures were more common among treated infants. The mortality rate was 14 per cent in the treatment group

and 13 per cent in the control one. There was only one death from infection and that infant's flora was not unusual. Finland[12] studied the nasopharyngeal bacteriology of premature infants in detail and pointed out the following: (1) The nasopharynx is sterile at birth in 80 to 90 per cent of premature infants. (2) Colonization—predominantly with staphylococci, *Streptococcus viridans*, Group A streptococci, and coliform organisms—takes place within 18 and 72 hours. (3) Prophylaxis with penicillin reduced the number of streptococci; prophylaxis with tetracycline, the coliform organisms. No regimen affected colonization with staphylococci. (4) Respiratory pathogens such as pneumococci and *Hemophilus influenzae* occurred, but rarely in this age group. (5) Staphylococci from patients receiving tetracycline were more resistant than were their counterparts from untreated infants.

Finally, it should be pointed out that antibiotics may be distinctly toxic in premature babies. This has been well documented with chloramphenicol, given in dosage greater than 25 mg. per kilogram.[10, 13] In addition, sulfisoxazole has been incriminated as a cause of kernicterus in premature infants.[14]

At the present time it is not known to what extent infection in the perinatal period can be controlled by administering antimicrobials to mothers immediately prior to delivery or to the infant immediately following parturition. The problem hinges in part at least upon a more precise definition of the circumstances which predispose to infection in the perinatal period. The definitive study of antibiotic prophylaxis in premature infants has yet to be performed.

PREVENTION OF BACTERIAL COMPLICATIONS OF ACUTE NONBACTERIAL DISEASES

Upper respiratory infections. There is ample evidence in the literature that antibiotics do not affect the course of uncomplicated upper respiratory infections unless they are caused by specific bacterial pathogens.[15] A controlled study of the effect of oral penicillin in a group of college students showed that the drug did not shorten hospitalization, diminish the extent of subjective discomfort, affect the febrile course, or the ultimate requirement for hospital care.[16]

If "sore throat" is the presenting symptom, antibiotic therapy is more likely to be effective since as many as two thirds of these patients harbor streptococci. The "blind" treatment of 121 such patients resulted in improvement in pyrexia only in patients in whom streptococci were cultured.[17] However, as has been pointed out, the treatment of streptococcal sore throat without a culture first being obtained is more a matter of convenience than necessity, since rheumatic fever can be successfully prevented in patients who remain untreated for several days.[18]

A certain small percentage of patients with nonbacterial upper respiratory infections do develop bacterial complications among which are otitis media, mastoiditis, sinusitis, peritonsillar cellulitis, pneumonia, and meningitis.[15] The causative pathogens of these secondary bacterial infections are usually Group A streptococci, pneumococci, hemolytic staphylococci, or influenza bacilli. It has been claimed that administration of antibiotics to patients, particularly children, with nonbacterial infections will prevent the secondary bacterial complications. For example, Karelitz[19] advises antibiotics in all children with viral influenza and virus pneumonia. More recently Hodes[20] has recommended antibiotics in children with influenzoid disease because of the occasional finding of staphylococcal pneumonia at autopsy. Our experience during the 1957-1958 influenza epidemic indicates, however, that antibiotics given early in the course did not prevent the development of lethal pneumonia.[21] While bacterial complications undoubtedly occur in some patients with influenza, the mere presence of bacteria in the lung at autopsy does not indicate that these bacteria were the cause of death. In fact, the majority of fatal cases observed by us were related to overwhelming virus infection in the lungs. Rogers and his associates[22] have had similar experience.

Finke[23] has made a strong case for the use of prophylactic antibiotics during the early phase of influenza, and claims that such a program in his hands decreased morbidity as measured by absenteeism in school children and adults. Most of the patients receiving prophylactic antibiotics in this group were subject to repeated pulmonary infection and had structural lung disease such as emphysema and bronchiectasis which is known to predispose to infection in the lung. It is not surprising that the results of antibiotic therapy in this particular group were favorable. As will be discussed later, it has been the general experience that patients with chronic lung disease treated at the first sign of an exacerbation improve strikingly. Furthermore, since no cultures were obtained in Finke's study, it is not clear whether his patients were merely receiving antibiotic therapy for an acute flare-up rather than antibiotic prophylaxis to prevent development of bacterial invasion. There is no argument, however, with Finke's plea for further controlled studies of antibiotic prophylaxis during epidemics of acute viral upper respiratory disease; such studies are badly needed.

Another point pertinent to this argument is that bacterial complications of upper respiratory infections, except in specialized groups or in those with chronic pulmonary disease, are quite rare. For example, none of 54 patients with upper respiratory disease, most of which was probably A^1 influenza, had bacterial complications.[24] In the same study, an additional 96 patients were given prophylaxis with either oxytetracycline or erythromycin; none in this group developed bacterial infections. However, fever, cough, and subjective well-being were not favorably affected by antibiotics.

Weinstein and his associates[25] made a study of infections occurring during chemotherapy. They termed these superinfections, which characteristically made their appearance in patients whose primary infection had responded to antibiotics. Mere changes in flora which commonly accompany antimicrobial therapy were not considered superinfections. Among 3,095 patients the incidence of these secondary infections was 2.19 per cent, and most occurred in the upper respiratory tract following viral diseases which mistakenly had been treated with antibiotics. Superinfections were most frequent following the use of broad-spectrum antibiotics and were least often noted after penicillin. Hemolytic staphylococci, *H. influenzae, E. coli,* Proteus, and Pseudomonas were the most common offenders. Since infections with these organisms may be exceedingly difficult to treat, it seems important to point out that in most instances superinfections caused by these bacteria are avoidable if antibiotics are dispensed with restraint when indications for their use are not clear-cut.

While not strictly in the field of prophylaxis, a word about pertussis seems in order. Finland and his associates[26] pointed out that whooping cough did not respond dramatically to the broad-spectrum antibiotics and was refractory to penicillin. Weinstein[27] reported that neither the tetracyclines nor chloramphenicol were very effective in ameliorating cough and only oxytetracycline consistently eradicated *Hemophilus pertussis.* More importantly, 6 of 19 patients treated with chlortetracycline developed superinfections. A similar experience was noted with chloramphenicol. Whereas bacterial complications following tetracycline therapy were noted in only 12 per cent, moniliasis was the most prominent side effect. Twenty-one per cent of untreated patients developed bacterial complications. The criteria for improvement in pertussis are so poorly defined that the ability of antibiotics to prevent secondary bacterial infections is probably the most useful parameter on which to base their efficacy. With the exception of oxytetracycline, the rate of secondary infections was higher in treated than untreated children. Furthermore, the appearance of potentially pathogenic gram-negative bacteria was disturbing. The superinfections with these microorganisms are likely to be more serious than pertussis.

Prophylaxis of measles. Measles is a com-

mon disease and bacterial complications are sufficiently frequent that a systematic attempt to prevent their occurrence seems reasonable. Two points of view have evolved: One, championed by Karelitz, argues that bacterial complications, specifically otitis media, pneumonia, cervical adenitis, and bronchitis, can be prevented by the administration of antimicrobial agents during the pre-eruptive and early eruptive stages; the other, held by Weinstein, suggests that antibiotics not only predispose to the development of more secondary infections but also that these infections are caused by bacteria more resistant and difficult to treat than those which are responsible for bacterial complications in untreated children with measles. The issue is not completely settled.

In one study,[28] Karelitz gave chlortetracycline and penicillin to 45 and 44 children, respectively, for periods of 5 days; a third group served as controls. The signs and symptoms of measles were not affected except for a slightly longer febrile course in the untreated group. There were 10 secondary infections in the untreated group, 5 in the chlortetracycline group, and only 1 among the children given penicillin. However, 30 per cent of the children in the chlortetracycline group had vomiting and diarrhea. In a subsequent report,[29] the same author claimed that benzathine penicillin was effective in reducing the bacterial complications of measles. A number of patients, however, were treated with benzathine penicillin for complications already present, making it difficult to separate prophylaxis from therapy. Furthermore, pneumonia developed in one child and staphylococcal sepsis in another during Bicillin prophylaxis. Although it is stated that 12 patients among the untreated controls developed otitis media, pneumonia, and diarrhea, it is conceivable that these complications were present at the time of admission in at least some of the children, and they should have been placed in the treatment group. This study has the disadvantage of attempting to evaluate *therapy* as well as *prophylaxis,* and thus does neither conclusively.

Weinstein[30] found that 30 per cent of pa- tients, who had received chemotherapy fo complications of measles at home, had in- fections when admitted to the hospital, whil only 15 per cent of 298 untreated patien with measles were admitted with suppurati disease. Furthermore, of 256 children wh were not treated at home, only 4.6 per cen developed infections in the hospital, whil among 78 in whom infection was present at the time of admission, superinfections oc- curred in 11.6 per cent. The bacterial flora in the untreated group consisted predominantly of pneumococci and beta-hemolytic streptococci, whereas the causative organisms of secondary infections in treated patients were mostly *H. influenzae* and staphylococci. These observations indicate that antimicrobial prophylaxis in measles may be hazardous, and at best, is not beneficial. In a subsequent communication, Karelitz[31] reinvestigated this problem, and, although he concluded that children who received antibiotics fared better than those who did not, the study was retrospective and the regimens not uniform. Bacterial complications of measles were generally more frequent in children of low-income families and in children under the age of 3 years. Superinfections did not occur although the bacterial changes which antedate superinfections, i.e., colonization with staphylococci and coliform organisms, were observed. The author states that measles should not be treated routinely with prophylactic chemotherapy—a retrenchment of his previous views—but that antibiotics should be used in very young infants, children, and adults with pulmonary or cardiac disease who develop measles, and in pregnant women.

Unfortunately, rubeola is not readily available for controlled experimentation since relatively few patients with this disease are treated in the hospital. The answer to the problem of antimicrobial prophylaxis in measles lies in a study employing human volunteers in a closed environment such as in orphanages or in homes for retarded children. A vaccine against measles is being tested under these conditions; it seems

reasonable to do the same with antimicrobial agents.

Paralytic poliomyelitis. It is common practice to administer antibiotics to patients with paralytic poliomyelitis, particularly to those in a respirator and/or with tracheostomies. Weinstein[32] did not find this practice helpful in preventing infection; among 165 patients with bulbar poliomyelitis 16 per cent of those who did not receive antibiotic agents developed secondary infections, whereas 53 per cent of 63 patients who received antibiotics had bacterial complications. It is quite likely, however, that the latter group consisted of more seriously ill patients. This does not gainsay the fact that antibiotics failed to prevent infections. Among the treated patients 22 per cent had pneumonia caused by Pseudomonas, hemolytic staphylococci, and *H. influenzae*. Only 6 per cent of the untreated group developed pulmonary infections and these were due to pneumococci and beta streptococci.

Jackson and associates[33] carried out a detailed study of the tracheal flora of patients with bulbar poliomyelitis and made the following valuable observations:

1. No drug was capable of preventing implantation of microorganisms into the sterile trachea; the rate of implantation was 43 per cent among treated patients and 63 per cent among controls.

2. Quantitative bacterial counts revealed a favorable change, i.e., a decrease in the number of bacteria, in the untreated group.

3. Enterococci were the most difficult to eradicate and were the most persistent.

4. Implantation of staphylococci was sometimes prevented or delayed by the use of 2 drugs.

5. Entry of Aerobactor and *E. coli* was aborted by the use of broad-spectrum antibiotics.

6. Polymyxin, or sulfisoxazole and streptomycin prevented implantation of Pseudomonas, while colonization with Proteus species was encouraged by this regimen.

7. Candida appeared 5 times as frequently when 3 antibiotics were used as when one was employed.

8. Pneumococci, streptococci, and *H. influenzae* were not present in the trachea of these patients irrespective of antibiotic therapy.

9. Regardless of the number and type of antibacterial agents used, the rate of implantation was only 33 per cent lower in the treated group and, once implanted, bacteria multiplied more rapidly in patients given broad-spectrum antibiotics.

10. The unfavorable alterations in bacterial flora during antibiotic therapy suggest that these drugs be withheld until overt infections appear. Although some of the organisms enumerated, particularly enterococci and gram-negative bacilli, are not ordinarily pathogens in the respiratory tract, they may be more hazardous in these patients because of the coexistence of atelectasis and paralysis of the muscles of respiration.

The experience at the Massachusetts General Hospital[34] during the 1955 poliomyelitis epidemic confirms this experience; prophylactic antibiotics were not capable of preventing colonization of the trachea by resistant staphylococci, and these bacteria accounted for serious infections in 15 of 16 patients, 12 of whom had received antimicrobic agents. These studies provide evidence that chemoprophylaxis in paralytic poliomyelitis is of no value.

Antibiotic prophylaxis in surgery.

A. General considerations. No topic has been subject to as spirited discussions among clinicians as the value of prophylactic antibiotic therapy in the prevention of postoperative complications, such as wound infections, and postoperative pneumonitis, and in the prevention of infections in the urinary tract following insertion of indwelling urethral catheters. The factors governing the development of postoperative wound infections are exceedingly complex and include aseptic technique, carrier states among surgical personnel, duration of operation, associated disease (for example, recent data[35] suggest that patients with cancer may be unusually susceptible to wound infections), and the like. Antibiotics, therefore, comprise only one of many influences on the host. Thus the effects of prophylactic chemo-

therapy per se on the development and course of postoperative infections are difficult to interpret. Another confusing aspect is that colonization has frequently not been distinguished from infection.[36] Thus the mere presence of microorganisms in or around a wound is, in itself, not evidence of infection.

The majority of instances of serious postoperative sepsis is caused by hemolytic staphylococci. Dineen[37] in a recent survey of postoperative infections comments that, with the exception of intestinal and urological surgery, more than 85 per cent of wound infections were due to these organisms. At the New York Hospital peaks in the infection rate were observed in 1949, 1952, and 1953, perhaps due to increased administration of tetracyclines. Howe[38] became alarmed at the progressive rise in postoperative staphylococcal infections at the Massachusetts Memorial Hospital between 1949 and 1952. Among ward patients the incidence of postoperative infections was 1.09 per cent in 1949 and 7.22 per cent in 1953. An increment of similar magnitude was observed among private patients. Antimicrobial prophylaxis was in common use during this 5-year period, and elimination of this practice, as well as adoption of more stringent aseptic techniques and removal of staphylococcal carriers from the operating theater, resulted in return of the infection rate to approximately 1 to 2 per cent. Although these observations do not establish a cause-and-effect relationship between antibiotic prophylaxis and incidence of wound infection, it is quite probable that the ubiquitous use of these agents on surgical wards plays an important role in the pathogenesis of infections with resistant organisms. Minchew[35] has produced evidence that staphylococci isolated from patients with postoperative infections were more resistant to antibiotics than their counterparts cultured from untreated patients. Barnes[39] compared the occurrence of sepsis in wounds following inguinal herniorrhaphies and abdominal hysterectomies during the 20-year period from 1937 to 1957 and found no increase during the antibiotic era. He attributes the rise in sepsis reported by others to factors other than antibiotics, specifically, the increasing age of patients undergoing operation and the magnitude of operative procedures being performed on poor-risk patients.

B. Abdominal surgery. It is generally agreed by authorities[40, 41] that antibiotics should not be employed in "clean" surgical cases. However, the definition of "clean" permits considerable leeway, and the indications for chemoprophylaxis encompass a large segment of surgical practice including operations associated with shock, burns, and elective procedures of the lower gastrointestinal and genitourinary systems; traumatic operations; bone and joint surgery; operations involving the lung, esophagus, or kidneys; oral surgery; surgical procedures on patients with indwelling urethral catheters; drainage of boils; and pre-existing valvular cardiac disease. In most instances our information is not sufficiently complete to evaluate these recommendations critically. Quite frequently they are based on uncontrolled clinical experience or on animal experiments which are not applicable because of differences in the bacteriologic flora and response to infection in the experimental host. Table I summarizes the experience of a number of authors with antibiotic prophylaxis for surgical procedures. Since postoperative complications were of multiple etiology and included—in addition to wound infections—fever, pulmonary infections, and vascular accidents, the data should be interpreted only in general terms. Such reservations are also indicated inasmuch as the antibiotic regimens differed considerably in the several studies. Nevertheless, the consistency of the results adds to their validity.

McKittrick[42] pointed out a number of years ago that patients given antibiotics following surgical procedures involving the upper gastrointestinal tract and the gall bladder did no better with respect to fever, incidence of wound infection, and pulmonary complications than did patients in whom these agents were not used. These results have been confirmed by several other surgeons both in this country[43, 47, 48] and in

Table I. Prophylaxis in surgery

Author	Year	Type of operation	No. cases		Complications (%)	
			Treatment	No treatment	Treatment	No treatment
McKittrick[42]	1954	Gastrectomy	35	29	28	20
		Gall bladder	24	33	33	15
		Colonic	21	21	10	28
Sanchez-Ubeda[43]	1958	Herniorrhaphy	90	93	8	1
		Saphenous ligation	46	41	8	5
		Lumbar sympathectomy	20	25	1	16
		Thyroidectomy	7	6	0	0
		Radical mastectomy	7	7	42	28
		Orthopedic	9	8	22	12
		Cholecystectomy	35	35	20	20
		Subtotal gastrectomy	28	29	25	21
		Colonic	13	12	31	33
Hasslinger[44]	1956	Gastrectomy	153	290	26	1
Linder[45]	1957	Gastrectomy	170	53	6.5*	5.6*
		Cholecystectomy	256	59	8.7*	8.7*
Paulino[46]	1959	Cholecystectomy	30	30	13	10
Hoerr[47]	1949	General	26	61	15	15
Barnes[48]	1959	General	449	558	16	7
		Gastrectomy 64				
		Thyroidectomy 88				
		Cholecystectomy 125				
		Mastectomy 43				
		Herniorrhaphy 167				
Barnes[39]	1959	Inguinal herniorrhaphy	264	1,242	3.3	4.1
		Abdominal hysterectomy	855	4,122	3.8	3.5
Tachdjian[49]	1957	Clean orthopedic	1,900	1,100	5.9	2.6
Appleton[50]	1956	Transurethral resection	36	40	47	53
Blahey[51]	1952	Gynecologic	44	492	58†	23†

*Wound infections only.

†Pyuria only.

Europe and South America[44-46] (Table I). Some of the studies also included herniorrhaphies, lumbar sympathectomies, venous ligations, thyroidectomies, and mastectomies; in none of the studies were postoperative complications prevented by antibiotics. In some instances infections were more serious in treated patients and were associated with resistant microorganisms.[43, 45]

In the case of gastric operation, it has been suggested that antibiotics may be of value if used selectively.[52] For example, in 75 per cent of 64 patients undergoing operation for duodenal ulcer, cultures of the stomach were sterile. By contrast, in patients with gastric ulcers, only 17 per cent had a sterile stomach flora, and potential pathogens were cultured in 21 per cent; furthermore, among patients with gastric carcinoma only 7 per cent had negative gastric cultures and 53 per cent had potential pathogens. Administration of 3.0 Gm. of oxytetracycline per day for 3 days preoperatively to 21 patients with positive gastric cultures resulted in sterilization of the flora in 57 per cent. However, when cultures were obtained for one week postoperatively from the gastric stumps of patients receiving antimicrobial prophylaxis, it was found that they were likely to be

colonized by resistant staphylococci, Proteus, and yeasts; no comment was made as to whether these organisms were responsible for superinfections.

It is now accepted practice to use antibiotics which are poorly absorbed from the gastrointestinal tract in preparation of patients for surgical procedures involving the large intestine. This practice is said to diminish formation of fistulas and abscesses and the development of peritonitis.[41] There is no doubt that the bowel can be sterilized effectively by a number of antibiotics of which neomycin and its analogues are probably the most effective[53]; in one study, a combination of neomycin and tetracycline given for 48 hours preoperatively was capable of completely eradicating intestinal bacteria in 90 per cent of patients.[54] The basis for the tenet that it is safer to operate on a sterile bowel stems mostly from the experiments of Cohn and co-workers[55, 56] who were able to protect dogs from the lethal effects of devascularized segments of bowel by pre- and postoperative administration of antibiotics into the lumen of the gut. The question may be raised, however, whether the integrity of the bowel's vascular supply rather than its freedom from bacteria is not the most important factor predisposing to infection. Whatever the answer to this question, the practice of administering nonabsorbable antibiotics is generally not attended by undesirable side effects such as excessive paralytic ileus, emergence of resistant strains, or a significant incidence of staphylococcal pseudomembranous enterocolitis. While a controlled study has not been performed, it is logical to consider operation of the bowel in the same light as operation of a grossly contaminated wound. In each instance an attempt to eradicate pathogens by local use of antibiotics seems reasonable.

C. Orthopedic surgery. Tachdjian's observations[49] on 3,000 orthopedic operations are of particular interest since they contradict the popular idea that orthopedic cases are more subject to infections than operations elsewhere, and require, therefore, prophylactic antibiotics. This author also demonstrated that secondary infections were most likely when penicillin or penicillin and streptomycin were employed prophylactically, but that no drug was effective in preventing postoperative infections. In an unpublished study,[63] vancomycin was given to patients with fractured hips to prevent staphylococcal osteomyelitis. While staphylococcal infection was prevented by this regimen several superinfections with gram-negative bacilli occurred. These were, in general, milder than the staphylococcal infections in untreated controls.

D. Urologic surgery. Bacteremia occurs frequently in urologic operation, particularly following transurethral resection of the prostate. For example, Scott[57] recorded an incidence of 63 per cent following a variety of urologic procedures. Creevy and Feeney[58] reported that 45 per cent of blood cultures obtained at the completion of 94 prostatic resections were positive. He was able to reduce bacteremia to approximately 20 per cent by the administration of chloramphenicol and sulfisoxazole but not of penicillin and streptomycin. It is not stated whether wound infections were diminished by any of these regimens; the mortality was very low in all groups. Of considerable importance was an incidence of bacteremia of only 10 per cent in patients with negative urine cultures preoperatively, whereas 57 per cent of those with urinary tract infections had postoperative invasion of the blood stream. On the other hand, another author[59] reports an incidence of bacteremia of only 1.56 per cent following 128 consecutive transurethral resections. Both cultures were positive for Pseudomonas; one patient had received antibiotics preoperatively, the other had not. Sixty-seven patients who had not been given antimicrobials had sterile blood cultures. These observations indicate clearly that prevention of bacteremia is not necessarily dependent upon the use of bacteriostatic agents, and they corroborate the data of Appleton and Waisbren[50] that prophylactic antibiotics in prostatic surgical procedures have no effect on postoperative complications, bacteremia, postoperative

drainage, pyrexia, duration of hospital stay, or mortality. Since subacute bacterial endocarditis following transurethral resection has been well documented,[18] prophylaxis as described in the third paper of this symposium is indicated. In patients without valvular heart disease, however, routine use of these drugs does not seem warranted.

E. Urethral catheterization. It is well known that symptomatic cystitis follows single catheterization in 2 to 5 per cent of patients and that asymptomatic bacteriuria may be much more common.[60] Whether this can be prevented by the administration of appropriate antimicrobial agents (sulfonamides or broad-spectrum antibiotics) is not clear and requires a carefully controlled study. Some recommend a short course of tetracycline following the single insertion of a urethral catheter; this may be of value in patients particularly susceptible to subacute bacterial endocarditis.

The use of the indwelling urethral catheter is followed by urinary tract infection within 48 hours in 98 per cent of patients.[60] Attempts to prevent bacilluria are commonplace and these patients more often than not are "covered with antibiotics." The efficacy of this practice was examined by Petersdorf and colleagues.[61] Thirty-eight patients receiving prophylactic penicillin and streptomycin, nitrofurantoin, or sulfisoxazole developed bacteriuria. In 17 of the 38 patients the urinary flora changed from *E. coli* or *A. aerogenes* to Proteus, Pseudomonas, or resistant *Staphylococcus aureus;* in other words, a relatively sensitive flora was replaced by a highly resistant one in nearly half of the cases. Among 11 patients with indwelling catheters, not receiving antibiotics, bacteriuria was present in all, but infection with more resistant bacteria supervened in only one instance. It is our practice not to employ antibiotics in catheterized patients unless evidence of sepsis appears; we then try to employ bacteriostatic agents only during the acute episode and hold the more potent bactericidal drugs in reserve until the catheter is removed. The urethral catheter acts as a foreign body; as long as it is present, infection cannot be eradicated. It seems futile to expend potent drugs unless chances for a definitive cure are reasonably good.

The use of antibiotics to prevent infection in patients undergoing catheterization is more often dictated by emotion than by factual knowledge. The following quotation[62] illustrates the prevailing noncritical attitude: "Evidence points to the futility of the use of chemoprophylaxis in these (catheterized) patients. I personally will continue to use maintenance doses of some drug, even if it does nothing but salve my conscience. The clinical well-being of the patient is important."

F. Gynecologic surgery. Blahey[51] administered 1.0 Gm. of oxytetracycline pre- and postoperatively to a group of patients undergoing vaginal hysterectomy and vaginal repair. Treated patients had a marked diminution in pyuria compared to untreated controls but other parameters including residual urine, bacteriuria, morbidity, and wound healing were not affected. The bacterial flora changed from *E. coli* and *A. aerogenes* to *B. proteus* and *Staph. aureus* in the women treated with Terramycin.

G. Cardiac surgery. This subject has been discussed in the preceding paper under prophylaxis against bacterial endocarditis.[18]

H. Thoracic surgery. Patients undergoing operative procedures involving transection of the bronchial tree which is rarely free of bacteria should probably be given prophylactic penicillin and streptomycin to prevent postoperative empyema or bronchopleural fistula; the relative effectiveness of this procedure remains to be established.

I. Burns. Infection, particularly bacteremia, has presented an insoluble problem in severly burned patients. Formerly, beta streptococcal infection was a serious threat but with the routine administration of penicillin and streptomycin to burned patients, infection is commonly due to staphylococci and gram-negative bacilli. Despite massive antibiotic prophylaxis, sepsis has accounted for death in from 45 to 55 per cent of burned patients.[64-66] Pseudomonas has been particularly troublesome; for example, in

Moncrief's series 9 of 17 patients with staphylococcal sepsis recovered, whereas only one of 18 with gram-negative bacteremia, predominantly Pseudomonas, recovered. These dismal results with routine penicillin-streptomycin prophylaxis suggest that it might be wise to abandon the prophylactic use of these drugs in the hope that bacteremia will be caused by bacteria more sensitive to available antibiotic agents.

Complications of pregnancy. Usually women in prolonged labor or with premature rupture of the membranes are given antibiotics primarily to prevent intrauterine infection and to reduce infant mortality. The effects of these drugs on the infant have been described in this paper[7, 8]; the general impression is that neonatal mortality and morbidity may be favorably affected. No mention is made of the maternal response. Presumably the process is self-limited and after delivery the infection terminates spontaneously in the majority of instances.

Kass[67] studied the effects of prophylactic antibiotic therapy in patients with bacteriuria during pregnancy. He found that 6 to 7 per cent of prospective mothers at the Boston City Hospital had significant bacteriuria. In the absence of therapy 40 per cent of these patients developed symptomatic pyelonephritis, whereas all those treated with sulfonamides to suppress bacterial growth in the urine remained free of symptoms. When examined several months after delivery, 15 of 19 patients who had not received prophylactic therapy had persistent bacteriuria; in the treated group only 3 of 14 had positive cultures. Prophylaxis also had a profound effect on the offspring of mothers with bacilluria: 17 per cent of infants born to bacteriuric mothers died during the perinatal period while 24 per cent of mothers had premature infants. These figures were 0 and 10 per cent in the treated group, and 2 and 9 per cent in mothers with sterile urines during pregnancy. These data indicate that the administration of prophylactic antimicrobials to mothers with bacteriuria will prevent occurrence of symptomatic pyelonephritis, postpartum bacteriuria, and may favorably influence the infant's chances for survival.

Acute cardiac failure. The frequent coexistence of pneumonia and pulmonary edema at autopsy, the similarity of these two entities clinically and radiologically, and the pathogenic relationships between these two processes, led Robin and Thomas[68] to suggest that antibiotics be used routinely in all patients with acute failure of the left ventricle. Petersdorf and Merchant[69] investigated this problem in a double-blind study employing chloramphenicol and a placebo. Chloramphenicol had no effect on the course of cardiac failure but treated patients tended to have somewhat less fever although their leukocyte counts were not affected. The case fatality rate was 29 per cent in the antibiotic group and 22 per cent in the controls; 11 per cent of the former and 7 per cent of the latter had pneumonia clinically or at autopsy. Among 14 patients with pulmonary infections, 4 recovered; in 6 the infection was an incidental finding not related to death, but in 4 (3 on chloramphenicol and 1 on the placebo) it was the major factor in death. Adverse reactions to chloramphenicol were noted in 6 patients and included severe staphylococcal enterocolitis in 2. These observations do not support the suggestion that antibiotics be given routinely to patients with acute cardiac failure. Instead, special care should be taken to discover pulmonary infection early and to treat it vigorously with an appropriate drug.

Comatose patients. The administration of antibiotics to comatose patients has become almost routine in many clinics. For example, Plum[70] attributes the low mortality rate among cases of barbiturate intoxication to the routine use of antibiotics. In a controlled study[61] 32 comatose patients with no overt infection were treated prophylactically with penicillin and streptomycin or with tetracycline and 10 with sulfisoxazole or nitrofurantoin; no antimicrobial prophylaxis was administered to the remaining 30. The mortality was not influenced by the antibiotic therapy; however, 45 per cent of the treated

group developed pneumonia, a complication observed in only 15 per cent of the controls. Seven of the treated patients had cutaneous staphylococcal infections and 2 died with gram-negative bacteremia. Chemoprophylaxis had no effect on the carrier rates of staphylococci, and strains isolated from the treated group were more resistant than were those cultured from controls. There was, in addition, a replacement of normal nasopharyngeal flora by gram-negative bacilli. These data support the thesis that prophylactic antibiotic therapy is of no benefit in these patients and may be distinctly hazardous.

ANTIMICROBIAL PROPHYLAXIS OF CHRONIC DISEASE

Cystic fibrosis. Pulmonary infections are the major problem in therapy of patients with cystic fibrosis and are responsible for death in 90 per cent of them. Prevention of these infections would obviously be of great benefit. Beginning in 1949, Shwachman and his associates[71] published a series of reports in which chlortetracycline and oxytetracycline[72] were said to reduce the number of intercurrent acute episodes and to improve the patient's general well-being, chronic cough, and ability to gain weight. Stowens[73] claimed that chlortetracycline improved nitrogen balance in these children.

The claims for the efficacy of these programs of prophylaxis are, in general, based on the fact that life has been prolonged. For example, in Shwachman's[74] series, the average age at death during the period from 1940 to 1948 was 12.8 months, whereas during the ensuing 5-year period, the children lived to an age of 45.2 months. These comparisons ignore the other advances in the therapy of this disease, and, although suggestive of antibacterial therapeutic effect, are not definitive. One of the difficulties is that the onset of pulmonary disease in these children is often so insidious that irreversible structural damage to the lung has already occurred by the time symptoms appear. Furthermore, there is no evidence that antibiotic therapy, even if given early, has prevented the occurrence of respiratory involvement.[74] The question must be raised, therefore, whether intermittent therapy for acute exacerbations of cough, sputum, and fever might not be just as effective as continuous, long-term chemotherapy.

It should also be emphasized that the primary problem in the lungs of children with cystic fibrosis is not the presence of bacteria but the mechanical obstacle presented by thick, tenacious sputum. This viscous material is a superb culture medium and could not be expected to remain free of bacteria; instead, with the eradication of the usual tracheobronchial flora, the bacteriologic vacuum is filled by resistant organisms and several authors have commented upon the appearance of nosocomial staphylococci[75] and Pseudomonas.[76]

The prevention of pulmonary infections in these children leaves much to be desired; superinfections have been severe and frequently lethal. At best, chemoprophylaxis is only a temporary stopgap in arresting the progress of this disease.[77]

Chronic bronchitis and bronchiectasis. Patients with chronic bronchitis and bronchiectasis are highly susceptible to intercurrent respiratory infections which lead to progressive deterioration in pulmonary function. In England, particularly, this has presented a major public health problem and exacerbations of chronic bronchitis have been a major cause of absenteeism during the winter months.[88] The factors instrumental in the pathogenesis of bronchitis are complex, but bacterial infections have been thought to be of prime importance. According to Brumfitt,[92] the lower respiratory passages which are normally sterile become colonized by *H. influenzae,* and these organisms have been found deep within the mucosa at autopsy.[93] In view of this bacterial component, a number of investigators have attempted by a variety of antibiotic regimens to reduce the severity of such symptoms as cough, sputum, febrile episodes, dyspnea, and disability. In general, prophylaxis has been carried out in three ways: (1) Long-term

Table II. Antimicrobial prophylaxis in chronic bronchitis

Author	*Year*	*Disease*	*No. of patients*	*Therapy*		*Better (%)*	*No change (%)*	*Wor (%*
				Drug	*Duration*			
Barach[78]	1952	Chronic bronchitis, bronchiectasis	120	Penicillin aerosol	2 to 5 weeks	87	13	
			24	Chlortetracycline	1 week	79	21	
			17	Oxytetracycline	1 week	94	6	
			35	Chloramphenicol	1 week	80	20	
May[79]	1953	Chronic bronchitis	22	Penicillin, streptomycin and/or chlortetracycline	5 to 7 days	100		
				Chloramphenicol	1 to 2 weeks		100	
McVay[80]	1953	Chronic bronchitis, bronchiectasis	21	Chlortetracycline	2 weeks to 2 months	90	10	
				Control		22	33	45
Douglas[81]	1957	Chronic bronchitis, bronchiectasis	131	Penicillin	5 to 7 days	60	40	
			23	Chloramphenicol	5 to 7 days	78	22	
			28	Oxytetracycline	5 to 7 days	57	43	
Edwards[82]	1957	Chronic bronchitis	6	Oxytetracycline	6 months	83	17	
			5	Sulfonamide	6 months	80	20	
			6	Influenza vaccine	6 months	0	100	
			7	Oxytetracycline, sulfonamide	6 months	70	30	
			8	Oxytetracycline, influenza vaccine	6 months	50	50	
			8	Oxytetracycline, sulfonamide, influenza vaccine	6 months	88	12	
			6	Sulfonamide, influenza vaccine	6 months	17	83	
			7	Control		30	70	
Elmes[83]	1957	Chronic bronchitis	42	Oxytetracycline (with exacerbations)	*5 to 7 days	+		
			46	Control				
Medical Subcommitte Report[84]	1957	Bronchiectasis	44	Oxytetracycline	12 months	60		
			38	Penicillin	12 months	42		
			40	Control		28		
Edwards[85]	1958	Chronic bronchitis	20	Oxytetracycline	18 months	75		
			15	Oxytetracycline	*5 to 7 days	73		
			7	Control		43	57	
Cherniak[86]	1959	Chronic bronchitis, bronchiectasis	67	Tetracycline	3 to 18 months	+		
				Penicillin G				
				Oleandomycin and tetracycline	3 to 18 months	±		
				Control	3 to 18 months	±		
Moyes[87]	1959	Chronic bronchitis	19	Erythromycin	*5 days		84	16
			22	Erythromycin	5 days every 4 weeks	23	59	18
			21	Tetracycline	*5 days	48	43	9
			25	Tetracycline	5 days every 4 weeks	60	8	32
Murdoch[88]	1959	Chronic bronchitis	12	Oleandomycin and tetracycline	3 months	90	10	
			11	Control		10	90	
			25	Oxytetracycline	3 months	92		8
			40	Control			50	50

Table II. Cont'd

Author	Year	Disease	No. of patients	Therapy		Better (%)	No change (%)	Worse (%)
				Drug	Duration			
Norman[89]	1960	Chronic bronchitis	39	Tetracycline	3 to 12 months	54	28	18
				Control		28	38	34
Berry[90]	1960	Chronic bronchitis	26	Oxytetracycline	5 days		+	
			27	Control				
Francis[91]	1960	Chronic bronchitis	226	Tetracycline	4 months	+		
				Penicillin V	4 months	+		
				Control				

*For exacerbations only.

therapy over a period of several months; (2) intermittent therapy for several days or a week each month; and (3) therapy only for exacerbations. The results obtained by several authors are summarized in Table II. Dosages of drugs differed considerably, but in general they were in the therapeutic range. Irrespective of the criteria employed to assess improvement in each series, the majority of authors reported that patients did better during or immediately following chemotherapy. In general, the tetracyclines were most effective, with penicillin and sulfonamides less consistently so. Erythromycin in conjunction with *H. influenzae* vaccine failed to produce improvement. The duration of prophylactic therapy did not seem to influence the results, and treatment of exacerbations appeared to be as effective as prolonged constant administration of drugs. This point, however, requires further investigation.

From the bacteriologic point of view, the results support the etiological role of *H. influenzae* in chronic bronchitis, for, with one exception,[87] there was excellent correlation between the clinical results and diminution of this organism in the sputum (Table III). As might be expected, the number of pneumococci was greatly reduced regardless of the agent used. It is noteworthy that colonization of the patients' respiratory tracts with resistant staphylococci and Pseudomonas, which has been such a problem during chemoprophylaxis in patients with cystic fibrosis, did not occur. This may be related to the fact that these patients were generally treated on an outpatient basis and were not exposed to the more virulent hospital flora. Although there was an increase in the number of coliform organisms, superinfections did not occur.

It is now generally accepted that antimicrobial prophylaxis benefits patients with chronic bronchitis. The most feasible method of administration of these drugs, the optimum dosage, and duration of therapy remain to be determined.

Chronic congestive cardiac failure. Because of the propensity of patients with cardiac disease to develop acute episodes of cardiac decompensation in association with acute infections, McVay, Sprunt, and Stern[94] gave 0.5 Gm. of chlortetracycline to 73 patients with chronic congestive cardiac failure; 76 patients received a placebo. Fifteen patients in the treated group died, while there were 19 deaths among the controls; bronchopneumonia was present in 1 of the former and 4 of the latter. Patients receiving antibiotics tended to have fewer respiratory symptoms, better appetite, and in a few instances just "felt better." There was also a slight decrease in the number of hospital admissions among treated patients during the period of the study. Ten of the chlortetracycline group developed diarrhea and pruritus ani. The bacterial flora of the two groups was similar at the end of the study except for an increased number of strains of Proteus and a slightly more resistant fecal flora among the treated patients.

Table III. Effect of antibiotics on tracheobronchial flora

Author	*Year*	*Treatment*	*Hemophilus influenzae*	*Pneumococcus*	*Staphylococcus*	*Coliforms*	*Proteus*	*Pseudomonas*	*Yeasts*
Barach[78]	1952	Penicillin aerosol		Decrease	No change	Increase	No change	No change	Increase
		Penicillin and streptomycin dust		Decrease	No change	Increase	No change		Increase
		Chlortetracycline, oxytetracycline, and chloramphenicol	Decrease	Decrease	Decrease	Decrease	Increase	No change	No change
May[79]	1953	Chloramphenicol or streptomycin	Decrease						
		Penicillin		Decrease					
		Chlortetracycline	No change						
McVay[80]	1953	Chlortetracycline		No change	Decrease	Increase	Increase	No change	No change
Douglas[81]	1957	Penicillin	Decrease	Decrease					
Elmes[83]	1957	Oxytetracycline	Decrease	Decrease		Increase			
Cherniak[86]	1959	Tetracycline	Decrease	Decrease	Decrease				Decrease
		Oleandomycin and tetracycline	No change	Decrease	Decrease				No change
		Penicillin	No change	Decrease	Decrease				
Murdoch[88]	1959	Oleandomycin and tetracycline	Decrease	Decrease	Decrease	No change			
		Oxytetracycline	Decrease	Decrease	No change	No change			
Moyes[87]	1959	Erythromycin	Decrease	No change	No change				
		Tetracycline	Decrease	No change	No change				
Norman[89]	1960	Tetracycline	Decrease	Decrease	No change	No change	No change	No change	No change

Although the authors contend that antibiotic prophylaxis in chronic heart failure is of definite value, the data do not support their contention in convincing fashion.

Diabetes mellitus. Patients with diabetes mellitus are highly susceptible to intercurrent infection, a form of stress likely to lead to severe metabolic derangements. Staphylococcal furunculosis, pyelonephritis, tuberculosis, moniliasis, and mucormycosis are examples of infections which are more common in diabetes. McVay and colleagues[95] tried to forestall bacterial infections in 94 diabetics by the administration of 0.5 Gm. of chlortetracycline a day; 95 patients received a placebo. There were 3 deaths, none from bacterial infections. Patients receiving an antibiotic had fewer respiratory infections. There was no difference in the degree of pyuria but bacteriuria was less common in the treated group. This finding is difficult to interpret since the urine cultures were obtained during chemotherapy, and it is quite likely that the drug exerted sufficient bacteriostatic action transiently to sterilize the urine. Patients receiving chlortetracycline were in the hospital for shorter periods than controls, but the number of hospital admissions were the same. Treated patients, in general, considered the state of their health "better." Whereas the results indicate some slight improvement, confirmatory evidence is needed.

In a retrospective analysis[96] the decreased mortality and incidence of postoperative sepsis in diabetic patients subjected to operation was attributed to penicillin prophylaxis. Although this may be the case, these two indices also improved in patients receiving no antibiotics during the same period.

Neoplastic disease. Minchew,[35] in a recent study of infections at The Johns Hopkins Hospital, found these infections to be more common in patients with cancer. This may be only a reflection of the debility of this group of patients. Huff and Petersdorf[97] studied the incidence and cause of fever in patients with neoplastic disease and found it to be related to infection, usually distal to some obstruction produced by the tumor.

Patients with leukemia and other tumors of the hematopoietic system frequently have fever without other manifestations of infection. While the elevation in temperature may result from the leukemic process per se, at least 65 per cent of 92 febrile episodes studied at the National Institutes of Health were associated with infection.[98] In most instances these infections were bacterial in origin, and it was these authors' opinion that patients with leukemia should be treated with large doses of penicillin, streptomycin, and chloramphenicol at the onset of fever. It is essential that blood cultures be obtained prior to the beginning of therapy since bacteremia with resistant gram-negative bacilli is a common finding.

In patients without fever there is nothing to be gained by the use of prophylactic chemotherapy even in patients with low leukocyte counts. Prophylaxis does not prevent occurrence of infections; 19 patients with leukemia developed Pseudomonas bacteremia under the cover of prophylactic chemotherapy.[99] The use of adrenal corticosteroids and antileukemic drugs probably enhances the risk of infection in these patients.

Acute renal failure and the nephrotic syndrome. In acute renal failure antibiotics should never be administered in the absence of definite evidence of infection.[100] Although overwhelming sepsis may be the terminal event in these patients, it is wiser to await its symptomatic manifestations, obtain cultures, and then administer the appropriate antimicrobial agent.

In the preantibiotic era, pneumococcal and streptococcal infections were the most important causes of death in children with the nephrotic syndrome. This has led to the widely adopted practice of giving prophylactic antibiotics to these children. While no controlled studies have been performed, most authorities recommend chemotherapy with penicillin and one of the tetracyclines during the active stages of nephrosis and whenever the patients are receiving adrenal hormones.[101-103] Superinfections occur but appear to be less common than in leukemia and cystic fibrosis. For example, in the pa-

tients with Pseudomonas bacteremia alluded to previously,[99] 19 had leukemia, 3 cystic fibrosis, and only 1 nephrosis.

It seems reasonable to direct prophylaxis in these patients against one or two sensitive gram-positive pathogens, i.e., pneumococcus and streptococcus. Therefore, the methods of prophylaxis in nephrotic children might logically resemble those employed in rheumatic fever which are safe, inexpensive, and not attended by superinfections. A secondary gain which might be derived from prophylactic chemotherapy in children with nephrosis is the prevention of acute respiratory infections which often trigger exacerbations of the nephrotic process. Unfortunately prophylaxis has not been effective in this respect and several authors report that children receiving penicillin or other antibiotics contracted colds followed by recurrence of proteinuria.[104, 105]

OTHER ALTERATIONS IN HOST RESISTANCE

Adrenal cortical hormones. The observation that adrenal cortical hormones may cause exacerbations of latent infection or, under certain conditions, predispose man and experimental animals to infection is well documented; the pros and cons of corticosteroid therapy in infections are beyond the scope of this paper and have been discussed admirably by Kass.[106] Gibbs and associates[107] studied the incidence of staphylococcal infection on the dermatological service at Bellevue Hospital and found the incidence to be 2.6 per cent in untreated patients, 7.3 per cent in patients given antibiotics alone, 11.9 per cent in those who received only adrenal steroids, and 45.1 per cent in those receiving both drugs. This study was devoid of bacteriologic data and it is not clear whether the groups are comparable.

Leukopenia. It is not known whether leukopenia per se predisposes to infection; most diseases in which granulocytopenia is a major manifestation, such as leukemia or Felty's syndrome, are characterized by a number of other changes in the internal environment which alter resistance. Nevertheless, acute agranulocytosis is often complicated by severe infections, usually involving the mouth and throat, and Lawrence[108] recommends penicillin therapy in all cases of acute agranulocytosis.

Irradiation. The data concerned with the effect of radiation on the susceptibility to infection are scanty. Smith[109] reported an increase in survival time of irradiated mice treated with streptomycin or oxytetracycline. Animals treated with penicillin, chloramphenicol, and a sulfonamide survived for a shorter time than controls. These results are difficult to apply to man. In all probability, patients receiving massive doses of x-ray therapy are more susceptible to infection, but the underlying disease is usually so severe that it alone may make them easy targets for invasion by pathogenic microorganisms.

COMMENT

It becomes clear from the foregoing discussion that the extensive use of antibiotics for prophylaxis is frequently not justified, and is based more on wishful thinking than on factual information. We have attempted to approach the subject from an unbiased point of view and to present our interpretation of the data and recommendations for prophylaxis only when the results are sufficiently clear cut to warrant these specific comments. In many instances we have expressed no opinion, leaving the reader to draw his own conclusions.

It should be pointed out that the use of antibiotics involves certain definite risks, namely, hypersensitivity reactions, toxic side effects, and superinfections. The benefits to be derived from chemoprophylaxis should be weighed against its potential hazards. Finally, we would like to reiterate that a few well-planned, well-controlled studies would go far in answering some of the questions raised in this report.

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Postinjection sciatic nerve palsies in infants and children

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IT IS the purpose of this paper to review 21 cases of sciatic palsy, associated with intragluteal injections, in pediatric patients. The pertinent literature is discussed. Some observations on the course of this complication of intramuscular injections will be offered and, on the basis of these observations, it will be suggested that the gluteal injection site be abandoned in small or debilitated patients.

MATERIALS

Clinical. All but 2 of the 21 cases of sciatic nerve palsy reported here were seen on the Pediatric Services of The Johns Hopkins Hospital and The Baltimore City Hospitals between 1956 and 1959. They are summarized in Table I. Undoubtedly others did not come to our attention. The palsies were assumed to be secondary to injection and not to some other cause, e.g., pressure palsy of the common peroneal nerve. In some instances, however, this factor cannot be completely ruled out. It was recognized that mononeuropathies may be found in association with various viral diseases (poliomyelitis, herpes zoster), intoxications (diphtheria, botulism, and heavy metals), diabetes mellitus and collagen vascular disease. No stigmas of these diseases were present in our cases and a history of buttock injection was present in all. To the best of our knowledge, neonatal asphyxia, abnormalities of presentation at birth, and intraumbilical arterial analeptic drugs[1, 2] were not involved in the reported cases.

Nine patients were well nourished or of normal birthweight with average nutrition. Sixteen were infants. Of these, 14 were 3 months old or less and many were premature.

There was no common underlying cause for which the injections were given. The cases included a wide variety of common pediatric illnesses, some serious, others less so.

The sciatic palsies began after single or multiple injections of antibiotic medications, either alone or in combination with other materials. In 2 instances (Table I, Nos. 12

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Table I

Case no.	*Initials and hospital*	*Age at time of diagnosis*	*Weight at time of diagnosis*	*Primary disease*	*Neurological signs at time of diagnosis*	
					Lateral division of sciatic nerve	*Medial division of sciatic nerve*
1.	J. W.*	3 days	4,449 grams	Conjunctivitis	Foot drop	Gastroc. weakness† No hamstring weakness Sensory loss
2.	G. J.‡	4 days	2,948 grams	Prophylactic antibiotics for mother's postpartum fever	No foot drop No sensory loss	No gastroc. weakness Hamstring weakness No sensory loss
3.	A. A.*	10 days	3,727 grams	Maxillary osteomyelitis	Foot drop Sensory loss	No gastroc. weakness No hamstring weakness No sensory loss
4.	A. S.‡	13-15 days	1,500 grams (birth weight)	Omphalitis	Foot drop Sensory loss	Gastroc. weakness Hamstring weakness No sensory loss
5.	B. L.‡	14 days	1,460 grams (birth weight)	Hyperbilirubinemia and prophylactic antibiotics	Foot drop Sensory loss	Gastroc. weakness No hamstring weakness Sensory loss
6.	B. Z.*	15 days	2,650 grams (birth weight)	Hyperbilirubinemia and (?) septicemia	Foot drop Sensory loss	Gastroc. weakness No hamstring weakness Sensory loss
7.	D. S.*	21 days	1,200 grams (birth weight)	Staphylococcal septicemia	Foot drop No sensory loss	Gastroc. weakness No hamstring weakness No sensory loss
8.	S. N.*	21 days	2,800 grams (birth weight)	Staphylococcal pneumonia	Foot drop Sensory loss	Gastroc. weakness No hamstring weakness Sensory loss
9.	L. L.*	1½ months	3,572 grams (birth weight)	Osteomyelitis and staphylococcal septicemia	Foot drop Sensory loss	No gastroc. weakness No hamstring weakness No sensory loss
10.	R. H.‡	<2 months	2,381 grams (birth weight)	Unknown	Foot drop Sensory loss	No gastroc. weakness Hamstring weakness No sensory loss
11.	S. M.‡	2 months	1,700 grams (birth weight)	Staphylococcal abscess	Foot drop No sensory loss	?Gastroc. weakness No hamstring weakness No sensory loss
12.	M. B.§	2 months	"Good nutrition"	Staphylococcal pneumonia and empyema	Foot drop No sensory loss	No gastroc. weakness No hamstring weakness No sensory loss
13.	E. W.‡	2½ months	1,842 grams (birth weight)	Staphylococcal pneumonia and empyema	Foot drop No sensory loss	No gastroc. weakness No hamstring weakness No sensory loss
14.	C. B.‡	3 months	1,600 grams (birth weight)	Sickle cell anemia with prophylactic antibiotics	Foot drop No sensory loss	No gastroc. weakness No hamstring weakness No sensory loss
15.	M. K.¶	8 months	2,240 grams (birth weight)	Unknown	Foot drop Sensory loss	No gastroc. weakness No hamstring weakness No sensory loss
16.	G. M.‡	19 months	1,786 grams (birth weight)	Acute tonsillitis	Foot drop No sensory loss	Gastroc. weakness No hamstring weakness No sensory loss

Length of follow-up	Gluteal scar or granuloma	Residual deficit		Growth arrest	Recovery time
		Incapacitation	Residual signs		
5 months	0	0	Slight foot drop Progressing satisfactorily at follow-up visit	+	> 5 months ?
10 months	Gluteal scar	0	Slight hamstring weakness	0	10 months
2⅔ years	Granuloma	+	Moderate foot drop	0	No recovery
8 months	Gluteal scar	0	No residual signs	+	5 months
1 week	0	Inadequate follow-up	Inadequate follow-up	+	?
5 months	0	±	Mild foot drop; mild gastroc. weakness	+	> 5 months ?
6 months	0	0	No residual signs	+	4½ months
12 months	Granuloma	+	Moderate foot drop; shortened Achilles tendon	0	>12 months ?
7 months	Granuloma	+	Marked foot drop; permanent contracture	0	No recovery
2 months	0	+	Moderate foot drop; improving when last seen	+	> 2 months ?
No follow-up	0	Inadequate follow-up	Inadequate follow-up	0	?
3 years	0	+	Marked foot drop; permanent contracture	0	No recovery
19 months	Granuloma	+	Marked foot drop; permanent contracture	0	No recovery
14 months	0	0	No residual signs	+	13 months
No follow-up	0	Inadequate follow-up	Inadequate follow-up	0	?
1½ months	0	±	Mild foot drop	+	> 1½ months ?

Table I. Cont'd

Case no.	*Initials and hospital*	*Age at time of diagnosis*	*Weight at time of diagnosis*	*Primary disease*	*Neurological signs at time of diagnosis*	
					Lateral division of sciatic nerve	*Medial division of sciatic nerve*
17.	T. A.*	3 years	"Normal"	Otitis media	Foot drop Sensory loss	No gastroc. weakness No hamstring weakness No sensory loss
18.	J. P.*	3 years	"Normal"	Otitis media	Foot drop	Gastroc. weakness Hamstring weakness No sensory loss
19.	H. S.‡	3½ years	"Undernourished"	Acute tonsillitis	Foot drop Sensory loss	Gastroc. weakness No hamstring weakness No sensory loss
20.	J. W.‡	10 years	"Small child"	Undiagnosed febrile disease	Foot drop No sensory loss	Gastroc. weakness No hamstring weakness No sensory loss
21.	C. B.*	11 years	"Poor nutrition"	Undiagnosed febrile disease	Foot drop Sensory loss	Gastroc. weakness Hamstring weakness Sensory loss

*The Johns Hopkins Hospital.
†Gastroc. weakness: equivalent to weakness and/or diminution or absence of ankle jerk.
‡Baltimore City Hospitals.
§Children's Hospital School.
¶Sinai Hospital.

and 15) unidentified materials were injected on multiple occasions.

In 15 cases (Table I, Nos. 1, 3, 5, 6, 8-11, 13, 16-21) penicillin was used alone or in combination with other antibiotic medications. Penicillin was not implicated in 4 instances (Table I, Nos. 2, 4, 7, and 14). Drugs implicated in the absence of penicillin, and in combination with each other, included chloramphenicol, erythromycin, vitamin K, and tetracycline.

Single antibiotics were administered in 7 instances; penicillin in 6 cases and tetracycline in one. Of the 6 patients who were given penicillin alone, 2 received one injection (Table I, Nos. 1 and 17), 2 received two injections (Table I, Nos. 16 and 19) and 2 received multiple injections (Table I, Nos. 11 and 18). One patient received multiple injections of tetracycline.

The clinical manifestations of sciatic damage varied considerably. In some instances the palsy was noted by the attending physician immediately or soon after a buttock injection. The abnormality of the affected limb was recognized by nurses or parents in other cases. In one case, the presenting complaint was diminished leg movement. The other 20 infants had conspicuous foot drop.

The infant with diminished leg movement showed hamstring weakness as the only sign of sciatic deficit. Many of the remaining 20 with an obvious lateral division motor deficit also had evidence of medial division damage. Of these, 5 had medial division sensory impairment, 11 showed calf weakness and/or diminished ankle jerk, and 4 hamstring weakness. Twelve of the 20 had sensory changes in lateral division distribution. In 7 instances (Table I, Nos. 1, 3, 6, 7, 9, 16, and 21) electromyographic studies were performed, but were not found to be of additional diagnostic or prognostic value.

Eighteen patients were available for follow-up and functional assessment over periods ranging up to 3 years. Six of these recovered completely within periods ranging from 24 hours to 13 months. Four showed no improvement after intervals varying between 7 and 36 months. In one of these cases, neurolysis was ineffectual 2½ years after onset (Table I, No. 12). The remainder showed partial recovery.

Length of follow-up	Gluteal scar or granuloma	Residual deficit		Growth arrest	Recovery time
		Incapacitation	Residual signs		
1½ weeks	0	0	No residual signs	0	1½ weeks
24 hours	0	0	No residual signs	0	<24 hours
4 months	0	±	Moderate to mild foot drop Progressing satisfactorily when last seen	+	> 4 months ?
13 months	0	0	No residual signs	0	13 months
9 months	Granuloma	+	Hamstring weakness Marked gastroc. weakness Anesthesia over heel	0	> 9 months ?

Of the 18 patients who were followed, 6 had a persistent paralysis of foot dorsiflexors which required bracing and/or physiotherapy for treatment or prevention of an equinovarus deformity. A mild foot drop limited the gait somewhat in 3 cases. One patient with anesthesia over the heel was admitted to the hospital twice for grafting of a trophic ulcer. The remainder were able to run and play without restriction and had no fixed orthopedic deformities or disabling sensory impairment.

Nine instances of pedal growth arrest (Fig. 1) were noted. All occurred in children who were under 3½ years of age at the time of sciatic injury. Both divisions of the sciatic nerve were involved in all 9 cases. The appearance of a small foot did not necessarily imply incapacitation.

Search was made for factors of prognostic value in the initial stages of the sciatic palsy, but the results were disappointing for the most part. It is true that prompt improvement within a few days usually led to complete recovery. Such rapid improvement was unhappily rare. It may also be of significance that the 4 patients with no recovery, all of whom had disabling residua, had involvement of the lateral division alone. Superficial scars or ulceration in the affected buttock cannot be said to have predictive value within this small series, since recovery ensued in the 2 instances in which they were found. However, deep granulomas of the affected buttock were of serious omen. Severe functional disability persisted in all 5 cases where they were noted.

Anatomic. Dissections of the gluteal region with exposure of the sciatic nerve were performed in 1,500 gram and 2,750 gram stillborn infants. A transverse section of the thigh at the juncture of the distal one third with the proximal two thirds was also made in the larger specimen. A scale drawing of the larger preparation with varying placements of a 1½ inch, 22 gauge needle is shown in Fig. 2.

The relatively small area of the infant buttock (Fig. 2) enhances the possibility of placement of a needle into or in the vicinity of the sciatic nerve. In both dissected specimens, the maximal depth of tissue covering the sciatic nerve was less than 1 cm.

In the lateral compartment of the thigh

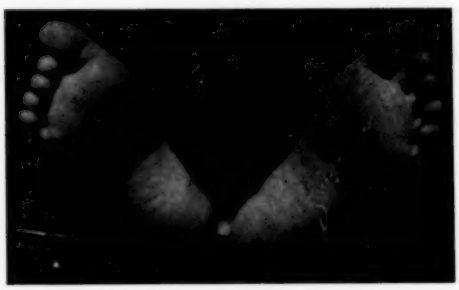

Fig. 1. Photograph of feet, revealing growth arrest of right foot following postinjection sciatic palsy.

there are no important neurovascular structures (Fig. 2). In the larger preparation, approximately 2 cm. of skin, subcutaneous tissue, and vastus lateralis muscle were noted overlying the femur.

DISCUSSION

Sciatic palsies secondary to injection into the gluteal mass have been recognized for at least 40 years.[3] Many pathogenic mechanisms have been postulated for the palsies appearing in infants, children, and adults in the course of extensive intramuscular therapy. These mechanisms include allergic peripheral neuritis, puncture of the nerve, ischemia of the nerve, and direct neural damage by drugs.

It is well recognized that peripheral nerve paralysis may occasionally occur in nerves distant from the injection site,[4] and an allergic mechanism has been postulated. In our cases, there was no clinical evidence of hypersensitivity to the medication being used. There were no instances of peripheral nerve palsies in nerves other than the sciatic nerve of the buttock receiving the injection, and all of our patients had received at least one injection into the appropriate buttock.

Experimentally, direct needling of the nerve in the newborn rat[5] and needling with procaine and saline in the cat,[6] rat,[5] and rabbit[7] does not cause significant neural degeneration.

The third postulated pathogenic mechanism is ischemia of the nerve, i.e., interruption of the vascular supply[8] or intraneural hemorrhage following needling. In one instance of sciatic palsy,[9] bismuth subsalicylate was found in local cutaneous arterioles following its injection into the gluteal region. This might suggest that concomitant emboli in vessels to the sciatic nerve produced the sciatic nerve palsy, since this cutaneous region and the sciatic nerve have a common regional blood supply.

The main intraneural longitudinal blood supply of the sciatic nerve is from the inferior gluteal artery, a branch of the external iliac artery.[1] In addition to this, there is an extraneural, regional supply directly from the external iliac artery which becomes dominant after birth.[1, 10, 11]

Ligature of the inferior gluteal artery in the rabbit is reported to have resulted in degeneration of the sciatic nerve.[12] Some investigators, however, have been unable to reproduce these degeneration experiments in the rabbit in other species unless the nerve underwent manipulation in addition to ligature of both regional and longitudinal arteries.[13] One study found that rupture of the inferior gluteal artery in the rabbit did not cause significant neural degeneration.[7] These authors also noted that the injection of autologous blood into the nerve produced minimal axonal degeneration. This experimental evidence would tend to minimize the vascular factor as an important pathogenic mechanism in human sciatic injection palsies. In our material, we found no evidence of large vessel impairment in the affected limb.

Direct injection of neurotoxic material into or near the nerve is, in our opinion, the most probable mechanism of sciatic nerve damage. In the neonate, infant, or debilitated pediatric patient it is extremely easy to inject into or near the sciatic nerve. The thickness of the protective layer of skin, subcutaneous tissue, and muscle over the sciatic nerve is such that it is well within the range of a standard needle, even if the needle is placed in the upper outer quadrant (Fig. 2). The majority of our patients were infants or were debilitated. In a squirming, uncooperative pediatric patient, slight

changes in angulation of the needle can easily result in injection into or near the sciatic nerve even if the skin is entered in the upper outer quadrant.

Among the drugs previously clinically implicated as neurotoxic agents are penicillin,[6, 7, 14, 15, 16] streptomycin,[6] antitoxins,[4, 17] vitamin B complex,[18] vitamin K,[1] bismuth,[9, 19] mercury,[19] quinine,[3] tetracycline,[20] and sulfisoxazole diethanolamine.[5]

Experimentally, many agents have been found to cause axonal degeneration and/or perineural scarring, when injected into or near the sciatic nerve of several species. A small but sound number of studies are available concerning this point.

Intraneural injection of penicillin, peanut oil, or penicillin in peanut oil causes axonal degeneration and fibroblastic proliferation in the dog, cat, and rabbit.[6, 7, 17] Intraneural injection of streptomycin, sesame oil, penicillin in sesame oil (cat),[6] or streptomycin (rabbit)[7] likewise results in axonal degeneration. On occasion, calcium deposits[7] and oil globules[6] have remained within the degenerated nerve.

Subepineural injection of crystalline penicillin, peanut oil, and streptomycin in the sciatic nerve of the cat[6] and rabbit[7] results in axonal degeneration. Sesame oil, calcium penicillin, potassium penicillin (cat),[6] and dihydrostreptomycin (rabbit)[7] also cause axonal degeneration when administered subepineurally.

Perineural administration of streptomycin under direct visual control causes dense perineural adhesions.[6] Coombes and Clark[5] reported that sulfisoxazole diethanolamine, tetracycline, oxytetracycline, erythromycin, tetracycline hydrochloride, and propylene

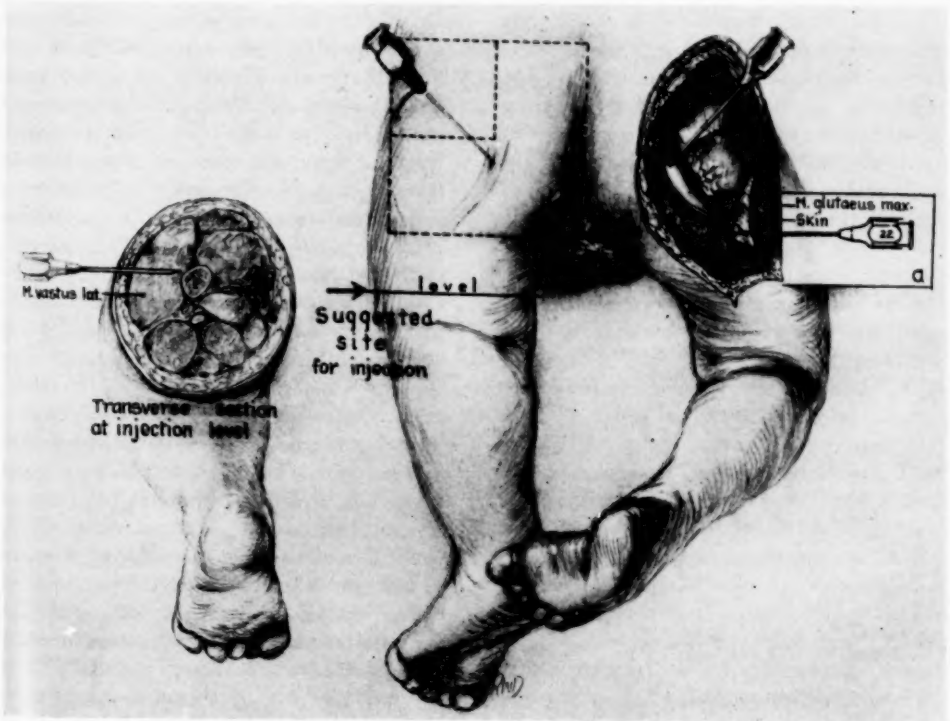

Fig. 2. Scale drawing of dissected buttock and transverse section of thigh. Varying placements of a 1½ inch, 22 gauge needle which show ease of inadvertent placement into sciatic nerve are depicted. The absence of important neurovascular structures in a lateral thigh placement is also shown.

glycol cause perineural adhesions when administered perineurally, but no definite statement was made regarding visual control of placement in these experiments.

Penicillin and tetracycline are the only two drugs which can be directly implicated as causes of sciatic injection palsy in our patients. In 2 instances single injections of penicillin were associated with sciatic palsy. In one case, multiple injections of tetracycline resulted in sciatic palsy. In the absence of these two agents, combinations of chloramphenicol, erythromycin, and vitamin K were associated with sciatic palsy.

It is apparent that a wide variety of medications have been clinically associated with sciatic palsy when injected into or near the nerve. Experimentally, many of the same drugs have been shown to be capable of causing axonal degeneration and/or fibroblastic proliferation. Thus, postinjection sciatic nerve damage has at least two prerequisites: the presence of a sufficiently neurotoxic material, and a certain proximity of the nerve to this material.

Trophic changes in the foot following experimental sciatic damage have been previously noted.[5] In half of our cases slight to moderate pedal growth arrest developed over the period of follow-up.

In all but 2 of our cases, the deficit was always more apparent in the lateral division. This reflects the long-recognized fact that the lateral division has less overlying protection than the medial one.[21]

The duration and degree of recovery are variable in the majority of reported cases of postinjection sciatic palsy. Recovery usually occurred within 6 weeks to 18 months,[2, 14, 15] but some cases required as long as 3 years.[22] One third (6) of our patients recovered completely within periods of 24 hours to 13 months. In 4 cases there was no recovery after intervals ranging between 7 and 36 months. The remaining 8 showed varying degrees of recovery.

There are divergent views regarding the treatment of postinjection sciatic palsies in infants and children. In a report on 2 patients, one of whom died within 2 months of the recognition of the sciatic injection palsy, Scheinberg[23] suggests nonsurgical treatment for a prolonged period. In opposition, Matson[24] favors early operative intervention. He reported 2 cases, one operated upon one year after onset of sciatic palsy, the second 3 weeks after onset, the improvement noted in the second case, "within the first few weeks of operation" with steady progression to a complete recovery "without deformity," was felt to substantiate the efficacy of neurolysis. Apparently this child began improving in about 6 weeks after the sciatic damage, a period not inconsistent with the onset of spontaneous improvement in some of our cases.

There are pathologic data to support each view. Thinning of the nerve without perineural adhesions was observed in one autopsied case of possible postinjection sciatic palsy.[25] This finding would support the conservative view of nonintervention. On the other hand, perineural adhesions are reported in some instances.[5, 24] We believe that careful palpation of the small buttock along the course of the sciatic nerve may offer a point of clinical differentiation between the cases with and those without dense perineural adhesions.

In our opinion, there are three objections to early neurolysis. One third of our patients recovered completely in periods ranging from 24 hours to 13 months. Unfortunately, in the initial stages of this condition we were unable to differentiate patients who would not require neurolysis from those who might potentially benefit from it. In experimental animals, much of the neurological incapacity may be attributed to axonal degeneration and intraneural scarring as well as to extraneural scar formation.[6, 7, 17] Neurolysis effects only the removal of extraneural scar tissue. Experimentally, the ischemic sciatic nerve does not necessarily undergo axonal degeneration unless it is manipulated.[13] Even though vascular factors are probably not important in the pathogenesis, one may question the wisdom of immediate operative manipulation of the sciatic nerve.

In our opinion, neurolysis should be performed in only two circumstances. In view of the ominous portent of deep granulomas in the buttock on the affected side, neurolysis should be performed relatively early when they are found. In all 5 of our cases with deep granulomas, there was a functionally disabling, neurological deficit. Superficial scars or ulcerations do not have this significance in our experience. The other circumstance in which neurolysis might be considered is that in which prolonged conservative care has not resulted in satisfactory improvement. Admittedly, we have no statistically significant experience with radical treatment of this entity. Our experience would indicate, however, that, in the absence of a deep granuloma, a period of 7 to 12 months without improvement should ensue prior to the performance of neurolysis.

More important than treatment of sciatic nerve palsy is the question of prevention. It is readily apparent from the number of cases presented that this complication of intramuscular therapy is relatively frequent in infants and small children. It must be remembered that the sciatic nerve is poorly protected in the infant so that inadvertent angulation of the needle in an uncooperative infant may result in injection of potentially neurotoxic agents into or near the sciatic nerve. In view of these considerations, the buttock should be abandoned as a site of injection in infants and debilitated children.

In the lower extremity there are three alternative sites for intramuscular injection. Two are unsatisfactory. The midanterior thigh[5] is not acceptable because of the ease of accidental puncture of important neurovascular structures lying anteromesial to the femur, especially in the proximal third of the femur. The lateral aspect of the hip[26, 27] may be adequate in the adult, but there is a definite danger of injection into the hip joint in infants and small children.[28]

The lateral aspect of the thigh, at the juncture of the distal third and proximal two thirds, offers a relatively large muscle mass without any important underlying neurovascular structures (Fig. 2). In the one specimen dissected, approximately 2 cm. of tissue were found overlying the femur.

Therefore, we strongly concur with the recommendation made by Turner[3] forty years ago ". . . that the region of the outer side of the thigh, where lies the great vastus externus muscle, is as nearly as possible the ideal place for all types of intramuscular injection."

SUMMARY

1. Twenty-one cases of postinjection sciatic palsy in infants and children are reviewed.

2. Penicillin and tetracycline are the only two antibiotics directly implicated, although multiple drugs were involved by association.

3. Immediate neurolysis is opposed in the majority of cases unless a deep granuloma can be felt in the buttock containing the affected nerve.

4. On the basis of anatomic, experimental, pathologic, and clinical observations, it is suggested that the buttock be abandoned as a site of injection in infants and children.

5. The lateral distal third of the thigh is recommended as a preferable injection site.

ADDENDUM

After the preparation of this paper, we have noted a publication by Coombes, Clark, and Gregory.[29] They, too, advise abandoning the buttock as a site for intramuscular injection.

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Viral meningoencephalitis

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FROM June to December, 1958, 44 patients were admitted to the St. Louis Children's Hospital in whom a presumptive clinical diagnosis of viral meningoencephalitis was made. From 31 of these children throat swab, stool, spinal fluid, acute and convalescent serum specimens were obtained and examined in the viral laboratory in an attempt to establish an exact etiological diagnosis. In 26 cases (84 per cent) an etiological diagnosis was established. The figure of 84 per cent compares favorably with the frequency in which an etiological diagnosis is made in children with bacterial meningitis.[1] A brief summary of the findings in this small group of patients will be made.

MATERIALS AND METHODS

Throat swab, stool, and spinal fluid specimens, after appropriate preparations,[2] were promptly inoculated onto HeLa and monkey kidney cell cultures. If cytopathic effect resulted, viral identification was performed by standard viral neutralization tests[3-6] in tissue culture by the use of known hyperimmune serums. Acute and convalescent serum specimens were titrated by established methods against the patient's own viral isolate for the presence of neutralizing antibodies. Serum specimens of patients from whom no virus was isolated were screened at a 1:8 dilution for the presence of complement-fixing antibodies against Eastern equine encephalitis, lymphocytic choriomeningitis, and mumps.[7]

RESULTS

From 31 patients with clinical meningoencephalitis, adequate specimens were obtained to warrant laboratory examination. Sixteen children were found to have poliomyelitis, and 15 of these exhibited clinical evidence of spinal cord involvement. Three showed signs of bulbar poliomyelitis, and one developed paralysis of the muscles of respiration. One patient, who had had no Salk vaccine, had nonparalytic poliomyelitis. Five of the patients with paralysis had received Salk vaccine, 2 of them having had 3 injections. In 1 of these 2 patients (Case 4) paralysis was limited to the left arm which had suffered a greenstick fracture 3 weeks prior to the onset of paralysis. Table I shows pertinent clinical data concerning this group of patients. Poliovirus Type I was isolated from all 16. The sources of viral

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Table I. History of Salk vaccine correlated with extent of paralysis

Case no.	*Age at onset of illness (yr.)*	*Salk immunization*		*Residual paralysis*	
		No.	*Date*	*Discharge*	*Follow-up*
1 (J. C.)	11	0		Quadriplegic weakness	Jan., 1960. Quadriplegic weakness. No change
2 (M. C.)	11/12	0		Facial weakness, right	Jan., 1960. Mild facial weakness, right. Improved
3 (D. D.)	5½	2	Dec., 1957 Jan., 1958	Flaccid left upper extremity	Jan., 1960. No residual
4 (P. D.)	6½	3	Jan., 1957 Feb., 1957 July, 1957	Flaccid left upper extremity	Feb., 1960. Flaccid left upper extremity. No change
5 (H. D.)	2	0		Hemiparesis, left; facial nerve paresis, left	March, 1960. Flaccid left arm, mild weakness left leg. Facial nerve, normal. Improved
6 (L. H.)	1½	1	Nov. 11, 1957	Lower extremities flaccid	No follow-up
7 (K. H.)	2	0		Normal	Normal
8 (R. L.)	4	0		Facial nerve paresis, right	March, 1960. Facial nerve weakness, right. Improved
9 (F. M.)	5 3/12	0		Paresis, lower extremities	No follow-up
10 (P. M.)	8	0		Died	
11 (I. M.)	9/12	0		Paresis, lower extremities	Feb., 1960. Flaccid right leg. Wears a brace. Improved
12 (D. O.)	2½	0		Paresis, left hip	March, 1960. Weakness and atrophy left hip. Improved
13 (M. P.)	7	2	Feb., 1958 March, 1958	Flaccid quadriplegia; respiratory paresis; transferred to Respiratory Center in California	No follow-up
14 (H. S.)	1 8/12	3	Dates not known	Lower extremities flaccid	Feb., 1960. Lower extremity weakness. Can walk with braces. Improved slightly
15 (C. S.)	6	0		Paresis, lower extremities	March, 1960. Weakness lower extremities. Improved
16 (B. T.)	3	0		Quadriplegia	March, 1960. Quadriplegia. No change

isolation and the results of serologic testing are summarized in Table II.

ECHO virus Type 9 was isolated from specimens obtained from 7 patients who were clinically ill with meningoencephalitis. ECHO virus Type 9 was isolated from the spinal fluid of 5 of these children. The spinal fluid findings in these patients are listed in Table III. Case 18 is interesting in that virus was isolated from the spinal fluid at a time when only 6 cells per cubic millimeter were present. There was no evidence of paralysis or muscle weakness in any of these patients at any time. At least a four-fold rise in neutralizing antibody titer to ECHO virus Type 9 was demonstrated in each of these patients.

One 13-month-old girl in this series had meningoencephalitis caused by Coxsackie virus B3. Although she exhibited weakness

in both lower extremities at the time of hospital admission she rapidly improved and showed no residual paralysis.

Two patients had mumps meningoencephalitis. At no time did they exhibit parotitis. Mumps virus was not isolated from either patient, but both had a greater than fourfold rise in complement-fixing antibody titer to the V-antigen of mumps virus.

Five other patients with meningoencephalitis were studied, but a viral etiological diagnosis could not be established.

DISCUSSION

The syndrome of aseptic meningitis was first described by Wallgren[8] in 1925. His original definition excluded poliomyelitis, mumps meningitis, and lymphocytic meningeal reactions associated with sinusitis and mastoiditis. Recent authorities[9-11] have tended to broaden the definition to include all conditions associated with a mononuclear cell meningeal reaction. Advances in viral methodology have disclosed that the syndrome is often caused by viral agents. The term viral meningitis or viral meningoencephalitis is appropriately applied to this group.

It is becoming increasingly evident that, when proper methods are employed a specific etiological diagnosis can be established in a high percentage of patients with viral meningoencephalitis. It is of prime importance to obtain the proper specimens from the patient, to collect them at the appropriate times in his clinical course, and to inoculate them promptly. Unless the complete group of throat swab, stool, spinal fluid, and serum specimens are available, the laboratory staff should not spend their time and effort in processing them only to arrive at an incomplete answer. In any study of a clinical syndrome, such as meningoencephalitis, one must consider the known viral agents which potentially can cause this disease pattern in man and also constantly be in search of new viral agents not previously associated with this type of illness.

Our experience in the isolation of poliovirus confirms that of Wenner and Miller[12] in so far as HeLa and monkey kidney tissue cultures are equally satisfactory for isolation of poliovirus from stools. With one exception monkey kidney cells were superior to HeLa cells for isolation of poliovirus from the oropharynx.

The rarity of isolation of poliovirus from the spinal fluid is well known. In Case 10 no virus was isolated from 2 specimens of spinal fluid. However, 24 hours later, at autopsy, poliovirus Type I was isolated from the medulla and from thoracic and lumbar spinal cord tissues. In contrast, in 5 of our 7 patients with ECHO virus Type 9 meningoencephalitis, the virus was isolated from the spinal fluid.

It is of interest to note the high titers of both neutralizing and complement-fixing antibodies to poliovirus Type I in the acute phase sera of the patients who had had prior Salk vaccine immunization. These patients had already developed paralysis at the time serum specimens from the acute phase were obtained. The antibody titers at the onset of the infections were possibly quite low, and viremia with nervous system involvement occurred before a protective level of poliovirus Type I antibody was achieved.

Fortunately, none of our patients with ECHO virus Type 9 meningoencephalitis had muscle paralysis, though this has been reported.[13] ECHO viruses Types 2, 3, 4, 5, 6, 9, 11, 14, 16, and 21 have all been associated with meningoencephalitis.[14, 15]

Coxsackie viruses Types B1 through B5 and Coxsackie viruses Types A7 and A9 have been shown to cause meningoencephalitis.[16-19] Coxsackie virus Type A7 has been reported to produce paralysis which cannot be differentiated clinically from that of poliomyelitis.[20]

SUMMARY

1. Thirty-one patients with meningoencephalitis were examined by standard virologic laboratory techniques. An etiological diagnosis was established in 26 of them.

2. Sixteen of the group were found to have poliomyelitis due to poliovirus Type I. Fifteen of the 16 had paralytic disease.

Table II. Virus isolation and antibody response

Case no.	Virus isolated	Residual paralysis	Polio shots	Source of virus: Throat MK	Throat HeLa	Stool MK	Stool HeLa	Cerebrospinal fluid MK	Cerebrospinal fluid HeLa	Tissue MK	Tissue HeLa	Neutralizing antibody to virus isolated		Complement-fixation poliovirus I		II	III
1 (J. C.)	Polio I	Yes	0	+	+	+	+	0	0	–	–	Ac	<4	Ac	<4	<4	<4
												Con	64	Con	4	<4	<4
2 (M. C.)	Polio I	Yes	0	+	+	+	+	0	0	–	–	Ac	16	Ac	<4	<4	<4
												Con	64	Con	64	<4	<4
3 (D. D.)	Polio I	Yes	2	+	0	+	+	0	0	–	–	Ac	256	Ac	16	<4	<4
												Con	1024	Con	16	<4	<4
4 (P. D.)	Polio I	Yes	3	+	+	+	+	0	0	–	–	Ac	256	Ac	64	4	<4
												Con	256	Con	16	4	<4
5 (H. D.)	Polio I	Yes	0	+	+	0	0	0	0	–	–	Ac	16				
												Con	64				
6 (L. H.)	Polio I	Yes	1	0	0	+	+	0	0	–	–	Ac	256				
												Con	1024				
7 (K. H.)	Polio I	No	0	+	+	–	–	0	0	–	–	Ac	64				
												Con	256				
8 (R. L.)	Polio I	Yes	0	+	0	+	+	0	0	–	–	Ac	<4	Ac	<4	<4	<4
												Con	64	Con	16	<4	<4
9 (F. M.)	Polio I	Yes	0	+	0	+	+	0	0	–	–	Ac	<4				
												Con	Not obtained				
10 (P. M.)	Polio I	Died	0	–	–	+	0	0	0	Medulla +	Medulla 0	Ac	<4				
												Con	Died				
										Thoracic spinal cord +	Thoracic spinal cord +						
										Lumbar spinal cord +	Lumbar spinal cord +						
										Cerebrum 0	Cerebrum 0						
										Mesenteric lymph nodes 0	Mesenteric lymph nodes 0						
										Liver 0	Liver 0						

										Liver 0	0						
										Myocardium 0	0						
11 (I. M.)	Polio I	Yes	0	0	+	+	+	0	0	–	–	Ac	16	Ac	<4	<4	<4
												Con	256	Con	16	<4	<4
12 (D. O.)	Polio I	Yes	0	+	0	+	+	–	–	–	–	Ac	16	Ac	<4	<4	<4
												Con	64	Con	16	<4	<4
13 (M. P.)	Polio I	Yes	2	0	0	+	+	0	0	–	–	Ac	256	Ac	64	64	<4
												Con	256	Con	16	4	<4
14 (H. S.)	Polio I	Yes	3	+	0	+	+	0	0	–	–	Ac	1024				
												Con	1024				
15 (C. S.)	Polio I	Yes	0	0	0	+	+	0	0	–	–	Ac	16				
												Con	256				
16 (B. T.)	Polio I	Yes	0	+	+	+	+	0	0	–	–	Ac	4				
												Con	Not obtained				
17 (E. B.)	ECHO 9	No	3	–	–	+	0	0	0	–	–	Ac	16				
												Con	64				
18 (A. C.)	ECHO 9	No	Not recorded	+	0	–	–	+	0	–	–	Ac	16				
												Con	1024				
19 (M. K.)	ECHO 9	No	4	–	–	–	–	+	0	–	–	Ac	4				
												Con	64				
20 (K. L.)	ECHO 9	No	3	+	0	0	0	–	–	–	–	Ac	16				
												Con	64				
21 (M. M.)	ECHO 9	No	Not recorded	+	0	–	–	+	0	–	–	Ac	4				
												Con	256				
22 (M. S.)	ECHO 9	No	4	+	0	+	0	+	0	–	–	Ac	<4				
												Con	16				
23 (C. W.)	ECHO 9	No	3	+	0	–	–	+	0	–	–	Ac	<4				
												Con	4096				
24 (L. S.)	Cox B3	No	0	+	0	+	0	0	0	–	–	Ac	4				
												Con	64				

+ = Virus isolated.
Ac = Acute phase serum.
– = No specimens.

0 = Virus not isolated.
Con = Convalescent phase serum.

Table III. Cerebrospinal fluid findings in patients in whom virus was isolated

Patient	*Cell count per mm³*	*Type of cells*	*Cerebrospinal fluid sugar (mg./100 ml.)*	*Cerebrospinal fluid protein (mg./100 ml.)*	*Cerebrospinal fluid chloride (mEq./L.)*	*Virus isolated*
18 (A. C.)	6	95% Mononuclear	77.6	64.2	135.0	ECHO 9
19 (M. K.)	96	60% Mononuclear	62.7	69.5		ECHO 9
21 (M. M.)	62	100% Mononuclear	55.6	46.6	118.0	ECHO 9
22 (M. S.)	188	95% Mononuclear	77.6	32.5	118.0	ECHO 9
23 (C. W.)	431	90% Mononuclear	71.4	59.0		ECHO 9

There was 1 death in this group. Five of the 16 patients had received Salk vaccine.

3. Infection caused by ECHO virus Type 9 was encountered in 7 patients.

4. Coxsackie virus Type B3 was isolated from 1 patient, and mumps virus was proved to be the etiological agent in 2.

5. In 5 patients the etiology could not be proved.

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Diamox in epilepsy

A critical review of 178 cases

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ACETAZOLEAMIDE (Diamox), a carbonic anhydrase inhibitor, has been used as an anticonvulsive agent since 1952. Both favorable and unfavorable results have been reported.

At The Blue Bird Circle Children's Clinic, Diamox has been used in more than 200 epileptic patients between 1954 and 1959. A review of our observations, including the indications, contraindications, therapeutic results, common side effects, and certain toxic manifestations, is presented in this report.

DEVELOPMENT AND MODE OF ACTION OF DIAMOX

In 1937 Cobb, Cohen, and Ney[1] found that certain vital dyes had an anticonvulsant action in experimental animals and in patients with epilepsy. Azosulfamide (Prontosil S) was one of the compounds they used.[2] In 1941 Cohen and Cobb[3] reported favorable results with this compound in about half of 10 epileptic patients. The mechanism of action was not known then.

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One year earlier, Mann and Keilin[4] had made an important observation in their study on carbonic anhydrase. They found that sulfanilamide had a powerful inhibiting effect on the action of the enzyme.

Cohen and Cobb, being familiar with the above work in their discussion on the anticonvulsive mechanism of Prontosil, commented: "of highest interest for speculation is the possibility that the effect produced is due to the property sulfanilamide possesses of inhibiting the action of carbonic anhydrase."

About the same time, Southworth[5] and Marshall, Cutting, and Kendall[6] demonstrated marked acidosis and alkaline diuresis following sulfonamide administration. This action is explained on the basis of sulfanilamide inhibition of renal carbonic anhydrase. Since this enzyme catalyzes the formation of H_2CO_3 in the equilibrium reaction:

$$CO_2 + H_2O \overset{CA}{\rightleftharpoons} H_2CO_3 \rightarrow H^+ + HCO_3^-$$

inhibition of the enzyme action decreases the rate of production of hydrogen ions. Normally as hydrogen ions are excreted, sodium ions are conserved. With a decrease in excretion of hydrogen ions, excretion of sodium ions is proportionately increased so as to maintain ionic balance. This leads to acidosis, diuresis, and alkaline urine.

Table I. Previous reports on Diamox in epilepsy

Author	*Year*	*No. of patients*	*Diamox alone*	*Dose (mg./Kg./day)*	*Duration of treatment in months*
Bergstrom et al.[9]	1952	42		10-30	
Merlis[13]	1954	47	13	28	11
Vivien[14]	1955	53		10-30	
Bordeleau[15]	1955	13			3-6
Ferroni et al.[16]	1955	14		750/day	4 days
Lombroso et al.[17]	1956	126	½ of cases	8-30	3-36
Ansell and Clarke[18]	1956	26	9	10	1.5-12
Millichap[19]	1956	14	2	18-36	
Livingston et al.[20]	1956	58	14	750/day	2-6
Golla and Sessions-Hodge[21]	1956	70		250-500/day	3+
Golla and Sessions-Hodge[22]	1957	78		250/day	3-10
Baird and Borofsky[23]	1957	16		1,000/day	1-3
Wada et al.[24]	1957	21	4	8-20	
Minde et al.[25]	1957	20	20		50 days
Holowach and Thurston[26]	1958	56		8-36	2-20
Ross[27]	1958	63		125-750/day	2-6

Schwartz[7] applied this phenomenon to cardiac patients with congestive heart failure with good results, but the toxicity of sulfonamide was a limiting factor.

In the search for a less toxic and more effective sulfonamide compound, Roblin and his associates[8] prepared the heterocyclic sulfonamide Diamox in 1950. The acidifying and dehydrating effects of Diamox led Bergstrom and co-workers[9] to its use in epilepsy, with some success. They believed that the action of the drug resembled that of a ketogenic diet. The acidosis and dehydration were found to be transitory, however, in spite of prolonged use of the drug. Although it was found that the carbonic anhydrase in the whole blood became readily inhibited, a correlation between clinical improvement and blood carbonic anhydrase activity could not be established. These observations suggested the possibility that inhibition of carbonic anhydrase in the brain, rather than systemic metabolic acidosis, was the mechanism of the anticonvulsive action.

Ashby[10] in 1944 had shown the presence of carbonic anhydrase in the nervous system in man. The enzyme was thought to hasten the removal of carbon dioxide incident to the firing of neurones, thereby accelerating the recovery of nerve sensibility. Inhibition of the enzyme results in the accumulation of carbon dioxide in the neurone and thus retards nervous conduction. This was confirmed by the following studies. Koch and Woodbury[11] concluded from their experiments in animals that carbonic anhydrase inhibitors exerted their anticonvulsant effect by increasing carbon dioxide tension in the cerebral neurone. This was substantiated by the demonstration of an increase in total carbon dioxide within the cells by actual tissue analysis following administration of Diamox.

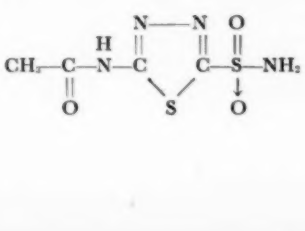
The observation of Millichap, Woodbury, and Goodman[12] that the anticonvulsant action of Diamox was not abolished by nephrectomy in mice further affirmed the direct action of Diamox on the brain cells.

CHEMICAL STRUCTURE

Acetazoleamide (Diamox), a sulfonamide derivative.

Empirical formula: $C_4H_6N_4O_3S_2$

2-acetylamino-1,3,4-thiadiazole-5-sulfonamide, a potent carbonic anhydrase inhibitor



Results (% of control)				
Good 80-100%	*Fair 50-80%*	*Poor 50% or less*	*Worse*	*Comments*
10	10		0	
62	13	25		Aged 19-64 years
11	22	20		
4	5	2		
	All improved			
37	17	46	0	
42		15		All had petit mal
75				Aged 6 months to 11 years
None. Only a few temporarily decreased in number of seizures				Aged 8 months to 14 years
25	43	2		Aged 6 to 35 years
43	Decrease in seizures in many of remainder			All petit mal seizures
		All		Only infantile myoclonic spasms
6	11			Aged 10 months to 40 years. Mental improvement
Reduced seizures in all when used with other drugs; Diamox alone of no help				Aged 3 months to 6 years. Some mental improvement
62.5	16	21.4		
2	No help in others			46 adults; 17 children

THE CLINICAL USE OF DIAMOX IN EPILEPSY

Bergstrom and co-workers[9] were the first investigators to use Diamox in the treatment of epileptic individuals. In 1952 they reported their results in 42 patients with intractable epilepsy. Their data showed excellent control in 10 per cent and moderate control in another 10 per cent; in none was the condition worsened.

Since then, 16 papers have been published, covering observations in a total of 717 patients. Table I summarizes the data of these reports. A more detailed review of these papers is impractical as the selection of patients (their age, sex, seizure types, etc.), the method of treatment, and the duration of therapy vary widely. It is not surprising that the results obtained were quite divergent. The following points are pertinent in relation to our findings:

1. With a few exceptions[20, 23, 27] the reported results of Diamox therapy are generally favorable.

2. Diamox alone as the sole anticonvulsive agent was effective in a small number of patients.[13, 17, 18] In most cases Diamox was combined with other anticonvulsants.

3. Merlis[13] and Lombroso and his associates[17] were impressed that the patients who showed marked alteration in their electroencephalogram upon overbreathing were helped most by Diamox. This correlation was not found, however, by Millichap,[19] Wada, Sato, and Morita,[24] and Holowach and Thurston.[26]

4. Merlis[13] reported that patients with autonomic seizures treated with large doses of Diamox alone were not helped and indeed were made worse.

5. Most workers agree that drug tolerance develops readily and to be effective the dosage should be increased to the maximal safe level.

6. The toxicity is low but blood changes and dermatoses have been recorded.

7. Some patients have shown improvement in mental and motor performance while on Diamox.

THE PRESENT STUDY

Selection of patients for Diamox treatment. We have had no rigid policy for the selection of patients for Diamox therapy. The present study is a retrospective rather than a designed investigation. Certain principles, however, have guided our decisions as to the use of Diamox in certain types of cases.

In the beginning, Diamox was used in the

more difficult or "refractory" cases. It was usually employed as an adjunct to the more conventional anticonvulsants regardless of the etiology and type of the seizures. In only a small number of cases have we used Diamox as the sole medication.

Because of frequent adverse gastric reactions, we have not used Diamox as freely in the very young or in infirm children whose appetite and nutrition were already precarious. In a period of 5 years, over 200 patients have received the drug. Of the 178 patients included in this study, 158 received Diamox in conjunction with other anticonvulsant drugs and 20 patients received Diamox alone. Excluded from the study is a group of 28 patients who developed sensitivity to the drug, causing the medication to be discontinued. Also excluded is another group of patients who were inadequately followed up.

The therapeutic response. In most of the 178 cases, Diamox had been continued from 6 months to 3 years. In a few cases, it was used only for 2 to 3 months. In the 158 cases where Diamox was used as an additional drug, the status of seizure control before the addition of Diamox served as the base line for the evaluation of therapeutic response. The number of attacks is used as the index of evaluation and the response is rated as follows:

Good—80 to 100 per cent seizure control.
Fair—50 to 80 per cent seizure control.
Poor—50 per cent control or not much change.
Worse—more seizures.

It is of interest to note that the mental status, sleep pattern, and general well-being of the child were often correlated with the degree of improvement in seizures.

Table II. Therapeutic response to Diamox

Degree of control	*No. of cases*
Good	76
Fair	44
Poor	55
Worse	3

Table III. Seizure type and therapeutic response to Diamox and anticonvulsants

Type	*No. of patients*	*Response*			
		Good	*Fair*	*Poor*	*Worse*
Convulsive equivalent	55	30	13	10	2
Symptomatic grand mal, petit mal types	50	17	12	21	0
Temporal lobe	20	8	6	6	0
Focal, other than temporal lobe; single focal and multifocal	28	8	8	11	1
Genetic or idiopathic, grand mal and petit mal	18	13	0	5	0
Massive spasms	7	0	5	2	0
Total	178	76	44	55	3

The over-all results of the entire series are shown in Table II.

Response of various types of seizures to Diamox. Inasmuch as every child seems to have a seizure pattern peculiar to himself, it is not easy to fit each child into a specific seizure type. As a general working formula, we have tried to group our patients in six seizure types* (Table III). There were 55 patients with convulsive equivalent type seizures†; 50 patients with grand mal and petit mal types of symptomatic epilepsy; 20 patients with temporal lobe seizures; 28 patients with other focal, non–temporal lobe seizures; 18 patients with genetic epilepsy; and 7 patients with massive spasms. The results of Diamox therapy summarized in Table III suggest that convulsive equivalent and genetic seizures are most responsive.

Electroencephalographic changes and response to Diamox therapy (Table IV). The

*The classification of seizure types is found in *Convulsive Disorders of Children*.[28]

†Convulsive equivalent seizures denote episodic manifestations of functional disturbances of the autonomic nervous system such as abdominal pain, vomiting, headache, chills, fever, and others. The term is synonymous with Gibbs' thalamic-hypothalamic epilepsy and Penfield's diencephalic-autonomic epilepsy.

most favorable response to Diamox therapy is noted in patients with the following electroencephalographic abnormalities: (1) paroxysmal 3 per second spike and wave dysrhythmia, (2) 14 and 6 per second positive spike discharges during sleep, without other abnormalities, (3) paroxysmal slow activity, (4) irregular slow occipital waves.

These abnormalities also correlate with the type of seizures that respond to Diamox therapy as shown in Table III. Thus, (1) is the pattern for genetic epilepsy and (2), (3), and (4) are those generally associated with convulsive equivalent seizures—the two types which responded most favorably to Diamox.

In a number of patients the abnormalities were brought out by sleep or overventilation. The data in Table V show that the response to Diamox was more favorable in cases showing the above electrographic changes. These observations are in agreement with the experience of Merlis[13] and Lombroso.[17]

About one-half of our patients had serial electroencephalographic examinations while on Diamox therapy. Ninety-six patients had follow-up electroencephalograms, with one-third showing definite improvement (Table VI). A larger number of patients who responded favorably to Diamox therapy showed improvement in their electroencephalograms, whereas more of those who responded poorly showed no change in the electroencephalographic picture.

Use of Diamox alone. Diamox was used alone in 20 cases. The type of seizures and the response to therapy are shown in Table VII. Six of 9 patients with convulsive equivalent type seizures showed good results.

Etiological factors of the epilepsies. In most instances the exact etiological factor causing the epilepsy could not be clearly established. Nevertheless, on the basis of detailed history, neurological examination, and laboratory examinations a presumptive etiological diagnosis was postulated and revised when indicated. Such attempts not only are of academic interest but were clinically important in guiding the treatment and prognosis.

Table VIII lists six major etiological categories in our group of patients. There were 48 cases in which the etiology was undetermined, 46 cases of birth injury (neonatal anoxia and trauma), 25 cases of sequelae of infection, and a miscellaneous group of 15 cases with such diverse etiology as dehydration thrombosis, lead encephalopathy, prematurity, developmental anomaly of the brain, cerebral lipidoses, and others.

As a general rule, the seizure pattern and not the etiological factor influences the choice of drugs in the treatment of epilepsy. However, Table VIII shows that genetic epilepsy responds more favorably to Diamox. It also shows that Diamox is effective in postnatal traumatic seizures, of which convulsive equivalent types are rather common.

Age and sex. No significant differences in response with respect to age or sex were

Table IV. Electroencephalographic changes and response to Diamox treatment

"Spontaneous" EEG findings	*No. of patients*	*Response to Diamox therapy*			
		Good	*Fair*	*Poor*	*Worse*
Normal	5	1	3	1	0
3/sec. paroxysmal spikewave activity	14	10	1	3	0
14 and 6/sec. positive spikes in sleep, without other abnormalities	10	8	1	1	0
Paroxysmal slow activity	15	9	2	4	0
Irregular occipital activity. Slow occipital activity. Fused occipital activity	14	8	5	0	1
Multifocal abnormality	28	13	9	6	0
Single focal abnormality	34	11	6	15	2
Paroxysmal spike-wave activity (not 3/sec.)	37	12	9	16	0
High-voltage slow activity	5	2	0	3	0
Fast activity	5	0	3	2	0
Hypsarrhythmia	9	1	5	3	0

Table V. Electroencephalographic abnormalities

EEG Finding	*No. of cases*	*Over-all results*					
		Marked reaction to overventilation			*14 and 6/second positive spikes*		
		Good	*Fair*	*Poor*	*Good*	*Fair*	*Poor*
Normal	5						
Paroxysmal 3/second spike-wave activity	14	2	0	0	0	0	0
Paroxysmal slow activity	15	4	0	1	2	0	1
Irregular slow fused occipital activity	14	1	2	0	4	0	0
Single focal abnormality	34	1	0	0	2	2	0
Multifocal abnormality	28	0	1	2	1	2	2
Paroxysmal spike-wave (not 3/second)	37	1	0	0	4	0	2
High-voltage slow	5	1	0	0	0	0	2
Fast activity	5	0	0	0	0	1	0
Hypsarrhythmia	9	0	0	0	0	0	0
Total		10	3	3	13	5	7

observed in our patients. In older girls, it is our experience that the use of Diamox 1 week to 10 days prior to each menstrual period helps to maintain better control of the seizures.

Dosage of Diamox. Our average dose is 15 to 30 mg. per kilogram per day. In a small number of patients the dose has been pushed as high as 40 mg. per kilogram per day with impunity. Drug tolerance develops in most instances. Therefore, one should not concede failure until the dose is increased to maximum tolerance levels.

Untoward reactions. Diamox is a relatively safe drug. The occurrence and severity of reactions are not linearly related to dosage levels. Individual susceptibility was a limiting factor in some of our patients. Table IX lists the untoward reactions we have encountered. The second column lists the reactions that forced us to stop medication. Some of these symptoms appeared as soon as 2 to 3 days after initiation of therapy. More likely they are manifestations of individual sensitivity (idiosyncrasy) rather than toxicity. The third column shows the common side effects, the most common being anorexia followed by drowsiness, vomiting, etc., in descending order. Agranulocytosis and severe dermatitis as reported by others[29, 30] have not been seen in our patients.

Table VI. Electroencephalographic findings after treatment

	No.	*Good*	*Fair*	*Poor*	*Worse*
Improved	32	18	8	6	0
No change	64	22	15	25	2
No follow-up EEG	80	34	21	24	1
Incomplete study —patient did not sleep	2	2	0	0	0
Total	178	76	44	55	3

DISCUSSION

In our experience, Diamox is one of the useful drugs in the treatment of all types of epilepsy. Used alone or as an adjuvant, Diamox may prove effective, especially for convulsive equivalent and genetic types of seizures.

The usefulness of Diamox in status epilepticus has been reported by Wada and coworkers.[24] Our experience was limted to a few patients in status epilepticus to whom Diamox was administered intravenously. Conclusions could not be drawn accurately, however, because in most instances other anticonvulsants were used concomitantly. In one instance a decrease in seizure discharge in the electroencephalogram was observed during intravenous injection of Diamox in an infant. Oral administration of Diamox was also initiated. The infant

Table VII. Response to Diamox alone

Type of seizures	Response			
	Good	Fair	Poor	Worse
Convulsive equivalent seizures	6	0	3	0
Genetic seizures	2	0	1	0
Symptomatic grand mal and petit mal seizures	3	1	4	0
Total	11	1	8	0

Table VIII. Possible etiological factor and response to Diamox therapy

Factor	No. of patients	Response			
		Good	Fair	Poor	Worse
Undetermined	48	21	12	15	0
Neonatal anoxia and birth trauma	46	13	17	14	2
Post infection	25	10	6	9	0
Postnatal trauma	24	15	5	3	1
Genetic (idiopathic)	20	13	0	7	0
Miscellaneous*	15	4	4	7	0
Total	178	76	44	55	3

*Miscellaneous: dehydration thrombosis, lead encephalopathy, prematurity, developmental anomaly of brain, cerebral lipidoses, and others.

Table IX. Side effects of Diamox

Symptom	No. of cases	Idiosyncrasy reaction, medication stopped	Mild reaction, medication continued
Anorexia	27	7	20
Drowsiness	11	4	7
Vomiting	10	3	7
Irritability	8	2	6
Headache	7	2	5
Fatigue	6	3	3
Dizziness	5	1	4
Enuresis	5	0	5
Paresthesia	4	3	1
Ataxia	3	0	3
Depression	3	3	0
Irregular respiration	2	0	2
Polyuria	2	0	2
Poor sleep	2	0	2
Skin rash	2	0	2
Abdominal distention	1	0	1
Cyanosis	1	0	1

remained seizure free for 3 days, when Diamox was discontinued because of extreme irritability. Saldias and collaborators[31] reported that intravenous administration of Diamox produced a marked reduction or total suppression of the abnormal discharges after hyperventilation in epileptic patients. Further observations on the intravenous use of Diamox alone in children with status epilepticus would be of great interest.

SUMMARY AND CONCLUSIONS

1. The literature on the development of Diamox, its mode of action, and its clinical use in epilepsy has been reviewed.

2. A series of 178 cases in which Diamox was used as adjuvant or sole treatment for epilepsy of various types at The Blue Bird Clinic has been analyzed and the therapeutic efficacy of the drug in correlation with different clinical factors has been critically evaluated.

3. The over-all therapeutic results were rated as good in 42.6 per cent (76 cases), fair in 24.7 per cent (44 cases), poor in 30.9 per cent (55 cases), worse in 3 cases.

4. Diamox was most effective in convulsive equivalent and genetic epilepsy.

5. Patients showing certain electroencephalographic abnormalities such as (a) paroxysmal 3 per second spike and wave dysrhythmia, (b) 14 and 6 per second positive spikes in sleep, (c) paroxysmal slow activity, and (d) irregular slow occipital activity responded more favorably to Diamox therapy.

6. Patients showing electroencephalographic abnormalities *brought out* by overventilation and sleep (14 and 6 per second positive spikes) were more responsive to Diamox therapy.

7. A good response to Diamox therapy was often followed by an improvement in electroencephalographic abnormality; a poor response by no change.

8. No significant difference was found between different age groups and the sexes in their response to Diamox therapy.

9. The average dose used was 15 to 30 mg. per kilogram per day.

10. Diamox is a safe agent. The most common untoward reaction among our children was anorexia. Infrequently, children may show idiosyncrasy to the drug.

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Initial tuberculous infection due to drug-resistant organisms

With a review of the world literature on initial infection due to isoniazid-resistant tubercle bacilli

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THE emergence of drug-resistant organisms following antimicrobial therapy has created new problems in the treatment of infectious diseases. In tuberculosis, strains of tubercle bacilli now exist which are resistant to one or more of the antimicrobial drugs currently in use.

The emergence of streptomycin-resistant strains has been associated with clinical and x-ray relapse, as well as reconversion to positive sputum, in the patients studied. Such strains readily produce tuberculous disease in susceptible animals. With the development of isoniazid resistance, however, the observation was made that many patients continue to do well clinically. The resistant organisms were found to have lost virulence for the guinea pig and mouse.[1, 2, 3] Middlebrook[4] noted that the tubercle bacillus, in the course of becoming isoniazid resistant, lost the action of the enzyme catalase normally present in the organism. He found that loss to be associated with loss of virulence in vivo. Other investigators,[5, 6, 7] however, observed great diversity among the isoniazid-resistant bacilli, and demonstrated that, in both guinea pig and mouse, they may produce lethal tuberculosis.

In view of the evidence cited above, it has become important to determine whether isoniazid-resistant organisms, *even if attenuated*, can produce tuberculosis in humans. It has been suggested by investigators in the field that the problem might best be resolved by studying children with primary tuberculosis, in whom the possibility of reinfection would not be a factor. Recognizing the importance of this problem, the Committee of the Section on Diseases of the Chest of the American Academy of Pediatrics conducted a survey among its members, representing 33 pediatric chest clinics throughout the United States, including Puerto Rico, to determine the incidence of isoniazid-resistant

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Table I. Cooperative study on primary tuberculosis in children caused by drug-resistant organisms

Total number of participating clinics		33
Number of clinics which culture gastric contents prior to onset of therapy		31
3 or more cultures	18	
1 to 3 cultures	8	
Number of cultures not stated	5	
Number of clinics which do *not* make drug susceptibility studies regularly		21
Number of clinics which make *no* drug susceptibility studies		3
Number of clinics which make drug susceptibility studies regularly on positive cultures		7
Total number of patients seen (approximate)		2,500
Number since introduction of isoniazid (approximate)		1,800
Percentage of positive cultures		10-90%
Total number of positive cultures (approximate)		325
Number positive since introduction of INH (approximate)		235
Number resistant to streptomycin		6
Number resistant to isoniazid		2
Number resistant to streptomycin and isoniazid		5

infection. A brief Committee report[8] was recently published, but a more detailed analysis seemed desirable, since this is the first report of initial infection with isoniazid-resistant tubercle bacilli from the United States. We were privileged to work on the original data and they were made available to us for the purpose of presenting a complete analysis of the results.

RESULTS

A total of 33 clinics, all actively engaged in the care of tuberculous children, participated in this survey. Table I gives the information received from these clinics. Although 31 of the 33 clinics obtained gastric cultures routinely prior to treatment, only 7 regularly tested susceptibility of the cultured organisms to drugs. It is the data from these 7 clinics which are analyzed in this report.

A total of 2,500 patients have been seen in these 7 clinics since the introduction of streptomycin therapy, 1,800 of whom were patients examined since the beginning of isoniazid treatment. Approximately 325 initially positive cultures (i.e., pretreatment) have been obtained from these patients since the introduction of streptomycin therapy, 235 since that of isoniazid. Of these, 6 were resistant to streptomycin, 2 to isoniazid, and 5 to both streptomycin and isoniazid, making a total of 13 patients resistant to one or both drugs.

Table II gives the pertinent findings in these 13 cases. For the purposes of this report, bacterial resistance to isoniazid was considered to be present if 1 per cent or more of the total population grew in 0.2 mcg. per milliliter of the drug; to streptomycin if 1 per cent or more of the total population grew in 2.0 mcg. per milliliter. Nevertheless, it may be seen from the table that most of the children showed far greater degrees of resistance than these minimal amounts. In 3 instances, the contact was known to have been resistant to the same drug as was the infected child. In 11 cases, the source of the culture was gastric contents, in one it was an abscess cavity, and in one a draining sinus. One patient died. He had progressive primary tuberculosis and cavitation, resistant to both drugs. All of the other children recovered. Although the catalase test was not done regularly, it was positive in the 3 isoniazid-resistant children on whom it was performed.

Brief summaries of the cases of infection with isoniazid-resistant organisms follow. The numbers refer to the case numbers in Table II.

Case 1. (From Presbyterian Hospital, New York City.) This was a boy with tuberculous meningitis whose initial gastric culture showed 4 plus resistance (i.e., indistinguishable from control) to 50 mcg. of isoniazid and 3 plus resistance (i.e., 75 per cent of control) to 100 mcg. of streptomycin. Spinal fluid on the same day showed 4 plus resistance to 50 mcg. of isoniazid and 3 plus resistance to 100 mcg. of streptomycin. The

cultures were catalase positive. The contact was the child's grandfather.

Case 2. (From Presbyterian Hospital, New York City.) This was a girl with primary tuberculosis whose first two gastric cultures showed 2 plus resistance (i.e., 50 per cent of control) to 0.5 mcg. and 3 colonies in 1 mcg. of isoniazid. She showed 4 plus resistance to 50 mcg. of streptomycin. One week later, she showed 3 plus resistance to 1 mcg. of isoniazid and 8 colonies in 5 mcg. of isoniazid. The cultures were catalase positive.

Case 3. (From the National Jewish Hospital, Denver, Colorado.) This patient was a 6-year-old girl infected by mother and aunt, the latter previously treated with isoniazid and streptomycin. The 4 initial cultures showed 4 plus resistance to 2 mcg. of streptomycin and 5 mcg. of isoniazid. The cultures were catalase positive.

The other isoniazid-resistant cases were from the Alejandro Ruiz Soler Sanatorium of Puerto Rico.

Case 8. A 1½-year-old infant with progressive primary tuberculosis had two pretreatment cultures resistant to 10 mcg. of isoniazid and 300 mcg. of streptomycin. He also showed resistance to 300 mcg. of viomycin and 25 mcg. of iproniazid. The contact was the mother. The patient died during the fifth month of hospitalization, in spite of treatment with isoniazid, streptomycin, and PAS.

Case 9. A 3½-year-old child had primary and skeletal tuberculosis with fistula formation. Culture obtained from the sinus tract prior to therapy was resistant to 10 mcg. of isoniazid and 25 mcg. of iproniazid.

Case 12. This was a 2-year-old child with primary tuberculosis, infected by the mother. Two pretreatment cultures were positive and resistant to 1.0 mcg. of isoniazid.

Table II. Cooperative study on primary tuberculosis in children—initial resistance to streptomycin and isoniazid

Diagnosis	*Resistance (mcg.)*		*Catalase test*	*Source of culture*	*Contact*
	Streptomycin	*Isoniazid*			
1. Tuberculous meningitis	100	50	+	Gastric+CSF	Grandfather
2. Primary tuberculosis	100	1	+	Gastric	Unknown
3. Primary tuberculosis	2	5	+	Gastric	Aunt treated with streptomycin, isoniazid
4. Primary tuberculosis*	Resistant	Susceptible	Not done	Gastric	Father resistant to streptomycin
5. Miliary tuberculosis	100	–†	Not done	Gastric	Unknown
6. Primary tuberculosis	10	Susceptible	Not done	Gastric	Father resistant to streptomycin
7. Primary tuberculosis	1000	Susceptible	Not done	Gastric	Grandmother resistant to streptomycin
8. Progressive primary tuberculosis with cavity‡	300	10	Not done	Gastric	Mother
9. Primary and skeletal tuberculosis§	Susceptible	10	Not done	Sinus	Unknown
10. Primary tuberculosis	100	Susceptible	Not done	Gastric	Mother
11. Progressive primary tuberculosis with cavity¶	300	Susceptible	Not done	Gastric	Grandmother
12. Primary tuberculosis	Susceptible	1	Not done	Gastric	Mother
13. Pott's disease‖	300	1	Not done	Abscess	Father

*Treated with streptomycin for 2 weeks prior to culture.
†Before the use of isoniazid.
‡Patient died in fifth month of treatment. Also resistant to viomycin and iproniazid.
§Also resistant to iproniazid.
¶Treated with streptomycin plus isoniazid 6 days prior to culture.
‖Treated with isoniazid plus PAS 9 days prior to culture.

Case 13. A 7-year-old child with Pott's disease had been infected by the father. Culture from the abscess on the ninth day of treatment with isoniazid and streptomycin was resistant to 1 mcg. isoniazid and 300 mcg. streptomycin.

It may be noted that in the Alejandro Ruiz Soler Sanatorium, where resistance to viomycin and iproniazid were also determined, cross-resistance to viomycin was seen in a child with streptomycin resistance and cross-resistance to iproniazid was seen in 2 children resistant to isoniazid.

In the 21 clinics which did not test drug susceptibility regularly, only 2 drug-resistant children were reported, a very small yield in comparison with that of the 7 clinics whose data are analyzed above. Both of these children (not included in Table II), one with primary tuberculosis and one with tuberculous meningitis, were resistant to streptomycin alone. Both had fathers who had been treated with streptomycin. Cultures were from gastric contents in the first child and cerebrospinal fluid in the second.

DISCUSSION

Although this study is the first in the United States reporting infection in children with isoniazid-resistant tubercle bacilli, several reports from Europe on such infection have appeared in the recent literature.

Table III. United States Veterans Administration Study. Incidence of tuberculous infection due to drug-resistant organisms in 3,161 veterans

Drug	Total No. of positive cultures	Resistant		Also resistant to		
		No.	%	Isoniazid (%)	PAS (%)	Streptomycin (%)
Streptomycin*	2,005	90	5	3	2	–
PAS*	2,005	143	8	3	–	2
Isoniazid†	2,005	117	6	–	3	3

*Organisms considered resistant if growth in 10 mcg. per milliliter is equal to growth of control.

†Organisms considered resistant if growth in 1 mcg. per milliliter is equal to growth of control *or* if there is any growth in 10 mcg. per milliliter.

Table IV. British Medical Research Council Study. Incidence of tuberculous infection due to drug-resistant organisms in 1,404 patients

Drug	Total No. of positive cultures	Resistant		Also resistant to		
		No.	%	Isoniazid (%)	PAS (%)	Streptomycin (%)
Streptomycin	974	22	2.3	0.1*	0.1	–
PAS	974	21	2.2	0.2	–	0.1*
Isoniazid	974	7	0.7	–	0.2	0.1*

*Represents one patient resistant to all three drugs.

The first, by Noufflard and associates,[9] states that, during a 5 year period at l'Hôpital Leon Bernard, 219 initial cultures were tested for susceptibility to isoniazid. Only one, a bovine strain isolated from a case of cervical adenitis, showed partial resistance to the drug, in a concentration of 2 mcg. per milliliter. This organism was catalase negative. The authors also describe an interesting case of a child with roentgen evidence of primary tuberculosis who was infected by an adult resistant to streptomycin and isoniazid. The child, however, had organisms which were streptomycin resistant but *sensitive* to isoniazid. Among the possible explanations suggested for this phenomenon is the one that isoniazid resistance disappeared following passage in the child. The experiments of Schmidt and associates[10] with monkeys may bear on this problem. They infected monkeys with pure cultures of strains known to be isoniazid resistant and catalase negative but were able to recover isoniazid-sensitive organisms from the animals. If resistant tubercle bacilli revert to a sensitive state in the host, that may explain the frequent success of isoniazid treatment in patients known to have isoniazid-resistant organisms.

In a second paper, Brissaud and associates[11] reported 2 cases of children infected with isoniazid-resistant organisms, one a patient with pleurisy and the other with mesenteric adenitis.

A third paper, by Debré and associates[2] includes the patients mentioned above,[9, 11] as

well as 2 other children with primary tuberculosis. Of the 4 resistant strains, 2 were attenuated for guinea pigs, all were catalase positive, and 2 were also resistant to streptomycin. All recovered uneventfully on isoniazid and PAS therapy.

A fourth report, by Esposti and Martoni,[13] describes 4 children with primary tuberculosis, 3 of whom had tuberculous meningitis, infected with resistant organisms. Two of the cultures were attenuated for guinea pigs, two virulent. The catalase test was not done. One of the children with meningitis, whose organisms were *attenuated* for guinea pigs, died.

Fouquet and associates[14] describe a child 2½ years of age with tuberculous meningitis, whose initial spinal fluid culture was resistant to both isoniazid and streptomycin, virulent for guinea pigs, and catalase positive. The patient was treated previously for primary tuberculosis with streptomycin and PAS but never with isoniazid. He recovered on isoniazid, streptomycin, and steroid therapy.

In addition, Klemm and Meissner[15] reported upon an infant 16 months of age with caseous pneumonia, infected by her father who had been treated with isoniazid. Both father and child are said to have had tubercle bacilli resistant to 50 mcg. per milliliter, catalase negative, and attenuated for guinea pigs.

In adults, there have been two large-scale cooperative studies of drug-resistant infections in presumably untreated patients. The results are summarized in Tables III and IV. In the United States Veterans Administration study[16] (Table III), 5 per cent of the positive cultures were found to be resistant to streptomycin, 6 per cent to isoniazid, and 8 per cent to PAS. Multiple drug resistance was present in 2 to 3 per cent of the cultures. It seems paradoxical that there was a greater percentage of infection with isoniazid-resistant organisms than with streptomycin-resistant ones. Perhaps this is a reflection of the wider use of isoniazid on an outpatient basis.

In the British Medical Research Council study[17] (Table IV), a lower order of resistance was found—2.3 per cent of the cultures were resistant to streptomycin, 0.4 per cent to isoniazid, and 2.2 per cent to PAS. Multiple drug resistance was present in 0.1 to 0.2 per cent. One of the isoniazid-resistant organisms was catalase negative.

Other reports of previously untreated adults infected with isoniazid-resistant organisms similarly suggest that these organisms can be virulent for man, even if attenuated in animals.[18, 19, 20] In considering the findings in adults, however, one must keep in mind the fact that it may be difficult to prove that these infections are, indeed, fresh and untreated.

In the present study, the proportion of children found to be infected with resistant organisms is about the same as it is in the studies of adults. There appears to be no appreciable difference in the incidence of isoniazid- and streptomycin-resistant tubercle bacilli. It is important to remember, however, that the percentage of positive cultures varied from one clinic to another and in a few clinics it was extremely low (i.e., 10 to 20 per cent positive). Perhaps, with better laboratory techniques, the yield of positive cultures can be increased. This will give more information on the state of resistance of the large majority of patients in whom positive cultures are not obtained at present. It is possible, indeed likely, that the total number of patients given in Table II represents only a fraction of the *real* total of patients with primary tuberculosis due to resistant organisms.

Whatever the final percentages may be, the most important fact to emerge from the studies on children with primary tuberculosis is that the principle of infection with isoniazid-resistant organisms, even when attenuated for animals, can be definitely established. In some instances the infection has terminated fatally. Undoubtedly there will be larger numbers of such infections with increasing use of the drug. It is essential, therefore, as a public health measure, to separate tuberculous patients who are still potentially infectious, whether or not they

are receiving drug therapy, from the uninfected. One cannot condone the early return of a mother to her family, for example, simply because she is being treated.

A rational approach to the treatment of the child with tuberculosis requires that cultures be obtained before therapy is begun and, if positive, tested for drug susceptibility. It is obvious from the present study that this is not done now with sufficient regularity. Furthermore, if resistance to isoniazid is demonstrated, it appears advisable to test the organism for catalase activity and pathogenicity in animals, in order to further our knowledge of the relationship between these factors and human infection. We would also profit by more conscientious testing for susceptibility of resistant organisms to related drugs. This would provide more data on the prevalence of cross-resistance. A comparison of initial resistance to isoniazid with resistance later in the course may yield important information about the effect of the host on the organism.

SUMMARY

A survey of pretreatment cultures in 2,500 children with primary tuberculosis from 7 pediatric chest clinics in the United States has revealed that, since the beginning of chemotherapy for tuberculosis, 7 children have been found to be infected initially with isoniazid-resistant tubercle bacilli and 11 children have been found to be infected initially with streptomycin-resistant organisms. The literature on tuberculous infection caused by isoniazid-resistant organisms is reviewed. The significance of such infections and the implications of these findings for future diagnostic and therapeutic management of tuberculosis are discussed.

We are indebted to the members of the Section on Diseases of the Chest of the American Academy of Pediatrics for making the information from their clinics available to us for this report.

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Intermittent peritoneal dialysis using 5 per cent albumin in the treatment of salicylate intoxication in children

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UTILIZING intermittent peritoneal dialysis, we recently demonstrated the effective removal of salicylate from acutely intoxicated dogs.[1] Grollman's solution, heparinized dog plasma, and 5 per cent human albumin in a buffered isoosmotic solution were employed as dialyzing fluids in these studies. The apparent binding of salicylate by the albumin in the latter 2 fluids resulted in elimination of considerably larger quantities of salicylate than that removed when the nonprotein electrolyte solution of Grollman was used. These results were sufficiently encouraging to prompt evaluation of this procedure in children with the use of albumin solution as the dialyzing medium. The ready availability of 5 per cent albumin, along with other advantages over plasma, renders this fluid the one of choice for the dialysis procedure. We wish to report our experience in 7 children with accidental salicylate intoxication who were treated with multiple peritoneal dialyses using 5 per cent albumin solution. In our opinion these patients were sufficiently benefited to justify a recommendation for use of peritoneal dialysis alone as a method of treatment. That use of this method in combination with others, such as exchange transfusion and/or judicious use of parenteral sodium bicarbonate, might be even more effective seems possible. The present study was designed primarily to evaluate the dialysis procedure per se as a means of ridding the body of salicylates.

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METHODS AND CLINICAL MATERIALS

Seven well-nourished and well-developed children ranging in age from 9 months to 44 months were included in this study. Four children received two consecutive dialyses and 3 received three consecutive dialyses each. All cases were examples of accidental poisoning and no illness was present at the time of ingestion of aspirin. The ingestion occurred from 6 to 24 hours prior to hospitalization and signs of toxicity such as nausea, listlessness, and rapid respiration had been present for 4 to 15 hours. At the time of admission all infants were lethargic, ranging from moderate in Patient 7 to severe in Patient 6. These patients were mildly to severely dehydrated and their temperatures ranged from 98.6° to 101° F. Kussmaul's respiratory patterns were present in all cases and respiratory rates varied between 36 and 64 per minute. The oral mucosa was parchmentlike and partially covered with dry, tenacious mucus. Blood pressures ranged from 90/40 to 110/70 mm. Hg and the heart rate from 120 to 152 per minute. Despite the lethargy, stimulation produced moderate hyperreactivity and occasional outbursts of crying and/or startle reaction occurred when aroused. All of the children had an anxious appearance. Vomiting, which had been present in all cases prior to hospitalization, continued in Patients 1 and 2 to whom water was given because of persistent thirst. No skin petechiae were observed. Vitamin K was given routinely to all patients promptly after the diagnosis of salicylism was established. The parents of only one patient knew of the salicylate ingestion prior to hospitalization, and they were unaware of its toxicity. In the remainder, only a later household investigation by the parents revealed ingestion of an unknown quantity of aspirin.

The clinical diagnosis of severe salicylate intoxication was confirmed promptly after admission to the hospital by plasma salicylate level determinations. These ranged from 40.4 mg. per cent to 62.3 mg. per cent (Table I). During the time that these studies were being conducted, 4 additional patients with mild to moderate clinical manifestations of salicylate intoxication and blood levels below 30 mg. per cent were admitted to the hospital but dialysis was not performed. These patients were treated with, and responded well to, parenteral fluid therapy which included alkali, sodium chloride, potassium, glucose, and water.

CASE SUMMARIES

Case 1. This 19-month-old Negro male, weighing 10 kilograms, ingested an unknown quantity of aspirin 11 hours prior to admission. Anorexia, lethargy, and vomiting followed 5 hours later. On admission he exhibited marked hyperventilation. Rectal temperature was 100.6° F.; cardiac rate, 130 per minute; blood pressure, 110/60 mm. Hg; and respiratory rate, 60 per minute. Dehydration was moderate. The remainder of the physical examination was not remarkable. Plasma salicylate was 41.0 mg. per cent. Two peritoneal lavages were performed over a 6-hour period. After 5 hours of dialysis, the respiration had improved markedly and the patient was alert and responsive.

Case 2. This 9-month-old Negro female weighing 9.75 kilograms, ingested an unknown quantity of aspirin 9½ hours prior to admission. Repeated vomiting, lethargy, irritability, and Kussmaul's respiratory pattern began 3 hours later. These findings were present on admission. Rectal temperature was 98.6° F.; respiratory rate, 48 per minute; cardiac rate, 144 per minute; blood pressure, 120/70 mm. Hg. The physical examination otherwise was not significant. Plasma salicylate was 62.3 mg. per cent. Two dialyses were performed over the next 7 hours. Because clinical improvement was so marked, no further dialysis was performed, even though the plasma salicylate was still 40.9 mg. per cent.

Case 3. This 30-month-old Negro female weighing 13.6 kilograms ingested an unknown quantity of aspirin 13½ hours prior to admission. This was followed 7 hours later by rapid respiration and repeated

Table I. Salicylate levels in plasma and dialysis fluid during dialyses

	Plasma							
	First dialysis				*Second dialysis*			
Hours	*0*	*1*	*2*	*3*	*1*	*2*	*3*	*1*
Patient 1 19 mo. 10 kg.	41.0	41.0	39.2	39.2	—	—	28.2	—
Patient 2 9 mo. 9.75 kg.	62.3	53.3	49.2	47.7	45.8	40.8	40.7	—
Patient 3 30 mo. 13.6 kg.	51.3	44.2	45.0	37.5	40.6	34.2	32.5	31.3
Patient 4 18 mo. 11.25 kg.	45.2	44.8	41.3	40.4	—	38.3	34.8	33.9
Patient 5 18 mo. 8.6 kg.	40.4	—	—	34.0	33.6	31.1	25.3	—
Patient 6 28 mo. 11.8 kg.	52.3	46.0	43.2	38.8	36.4	34.0	31.2	30.6
Patient 7 44 mo. 14.5 kg.	42.2	37.4	38.7	30.9	28.7	26.1	24.4	—

vomiting. Physical examination revealed irritability and marked hyperventilation. The rectal temperature was 100° F.; cardiac rate, 120 per minute; blood pressure, 110/80 mm. Hg; and respiratory rate, 33 per minute. Skin turgor was poor and oral mucosa was dry. The examination was otherwise normal. Plasma salicylate was 51.3 mg. per cent. Three dialyses were performed over the next 11 hours. After 6 hours clinical improvement was noted and progressed rapidly, with disappearance of lethargy and return of respiration to normal.

Case 4. This 18-month-old Negro male, weighing 11.25 kilograms, ingested an unknown quantity of aspirin 24 hours prior to admission. During the 12 hours immediately before admission, increased respiratory rate developed, along with vomiting and lethargy. On admission rectal temperature was 99° F.; cardiac rate, 120 per minute; blood pressure, 90/40 mm. Hg; and respiratory rate, 64 per minute. The infant was critically ill with rapid and deep respiration. He was severely dehydrated, with extremely dry mucous membranes. Plasma salicylate was 45.2 mg. per cent. Three peritoneal lavages were performed during the next 9½ hours. Clinical improvement was slower in this case but the patient reached a near-normal state 16 hours after initiation of therapy.

Case 5. This 18-month-old Negro male, weighing 8.75 kilograms, ingested an unknown quantity of aspirin 11 hours prior to admission. He was brought to the hospital 3 hours later because of vomiting. On admisson he was moderately lethargic and hyperventilating. Rectal temperature was 100.4° F.; cardiac rate, 140 per minute; blood pressure, 92/54 mm. Hg; and respiratory rate, 40 per minute. Dehydration was moderate. Physical examination was otherwise nonrevealing. Plasma salicylate was 40.4 mg. per cent. Two dialyses were performed over the next 6 hours, by the end of which time respiration was normal and the patient was alert.

Case 6. This 2-year-old white male, weighing 11.6 kilograms, ingested an unknown quantity of aspirin 24 hours before admission. Vomiting began 2 hours later. Rapid deep respiration and hyperkinesis followed 9 hours after ingestion of aspirin. He was

Third dialysis			Dialysis fluid								
			First dialysis			Second dialysis			Third dialysis		
1	2	3	1	2	3	1	2	3	1	2	3
—	—	—	8.2	20.5	29.8	—	—	32.6	—	—	—
—	—	—	10.5	28.8	36.2	21.1	25.1	40.9	—	—	—
31.3	29.1	23.0	6.5	13.5	19.2	5.3	12.7	15.2	8.6	11.0	14.7
33.9	29.1	24.8	10.9	19.1	26.5	14.8	20.4	26.3	7.4	13.3	14.8
—	—	—	14.5	27.7	30.2	11.9	15.7	16.6	—	—	—
30.6	28.1	27.7	—	—	23.6	—	—	31.9	—	—	21.3
—	—	—	8.6	13.1	18.8	6.5	11.4	15.0	—	—	—

critically ill on admission, with stupor, hyperkinesis, extreme Kussmaul respiration, and severe dehydration with drying of the oral mucosa. Temperature was 99.2° F.; cardiac rate, 152 per minute; blood pressure, 95/50 mm. Hg; and respiratory rate 52 per minute. Plasma salicylate was 52.3 mg. per cent. Three dialysis procedures were performed over the next 10 hours, with marked improvement beginning after 7 hours, and progressing rapidly to normal respiration and sensorium.

Case 7. This 44-month-old white male, weighing 14.5 kilograms, ingested an unknown quantity of aspirin 6 hours prior to admission. Two hours following ingestion he became lethargic, vomited, and began to breathe rapidly and deeply. On admission he was moderately ill, with Kussmaul's respiratory pattern and mild dehydration. Temperature was 101° F., rectally; cardiac rate, 140 per minute; blood pressure, 115/70 mm. Hg; and respiratory rate, 36 per minute. No other physical abnormalities were present. Plasma salicylate level was 49.6 mg. per cent. Two dialysis procedures were performed over the next 6 hours with rapid improvement in the patient's physical condition.

DIALYSIS PROCEDURE

Strict asepsis was practiced during the entire process. The bladder was emptied and an indwelling Foley catheter was allowed to remain in the bladder throughout the procedure. At a point one third the distance from the umbilicus to the symphysis pubis, the skin and anterior abdominal wall were anesthetized with 1 per cent procaine solution. With a No. 11 Bard-Parker blade, a small incision (3 to 4 mm.) was made through the skin and extended into the subcutaneous tissue without entering the peritoneal cavity. A No. 16 Fr. Ochsner trocar (stylet in place) was inserted into the abdominal cavity and the stylet was withdrawn. A multiperforated plastic catheter, as described by Maxwell and associates,[2] was inserted through the trocar and directed into the pelvic gutter. With the catheter held in place, the trocar was removed. By means of purse-string and mattress sutures or skin clips the abdominal wall was brought in snug apposition with the catheter. The en-

tire area was then covered with a sterile dressing which was not taken off until the final dialysis procedure was terminated.

Five per cent albumin in an isoosmotic buffered diluent (Albumisol)* was introduced into the peritoneal cavity in Case 1 in quantities equal to the calculated plasma volume, i.e., 5 per cent body weight, or 50 ml. per kilogram. In subsequent patients, as we gained experience and as more liberal quantities of Albumisol became available, we literally filled the abdominal cavity to the point of discomfort to the patient, at the same time being careful not to impede respiration and interfere with the respiratory adjustment of acid/base balance. The quantities of albumin solution used in each individual dialysis in Cases 2 to 6 ranged from 750 to 1,500 ml., corresponding to 60 to 105 ml. per kilogram and approximating from 1.2 to 2.5 times the plasma volume of the patients. The total volume of fluid used in each patient during all dialyses varied from 1,000 ml. in Patient 1 to 4,500 ml. in Patient 6. Five mEq. per liter of potassium, as potassium chloride, was added to the dialyzing fluid; also, 250 units of heparin were introduced into each 500 ml. flask of Albumisol prior to instillation in order to minimize formation of small aggregates of fibrin which could obstruct the perforations in the catheter. The fluid was then permitted to run rapidly into the peritoneal cavity by gravity in a period not exceeding 20 minutes. Empty 500 ml. flasks and the tubing were kept sterile for the purpose of collecting the return fluid by gravity. The quantity of fluid recovered ranged from 80 to 100 per cent of that introduced into the peritoneal cavity. Rather than adding antibiotics to the lavage fluid, the patients were given broad-spectrum antibiotics for 2 days following the procedure. No signs of peritonitis appeared, and we question the need for such antibiotic administration.

Because our experience with dogs[1] showed equilibration between blood and dialysis fluid within 3 hours, the dialyzing fluid was permitted to remain in the peritoneal cavity for this length of time before removal. The dialyzing procedure was carried out 2 or 3 times in each patient requiring a total time of approximately 6 to 11 hours. Samples of blood and peritoneal fluid were withdrawn at approximately hourly intervals and analyzed for salicylate, protein, K^+, Na^+, Ca^{++}, and HCO_3 concentrations and for pH and osmolarity.

Comprehensive clinical records were kept on the patients, giving particular attention to temperature, blood pressure, heart rate, respiratory rate and pattern, and central nervous system signs and symptoms.

Because of the desire to evaluate the role of peritoneal dialysis per se as a means of irradicating salicylate from the body, fluid therapy in Cases 1, 2, 3, 4, 5, and 7 consisted of initial hydration with M/12 sodium lactate, 360 ml. per square meter in 45 minutes, followed by 2,400 to 3,000 ml per square meter per 24 hours of Butler-Talbot solution with 5 per cent glucose. During the periods of dialysis this regimen resulted in continued excretion of an acid urine (pH 5 to 5.5) and relatively small total amounts of salicylate ranging from 41.5 to 117 mg. (Table II). (In Patient 6, as will be mentioned later, more liberal quantities of $NaHCO_3$ were given.) Midway during the procedure each patient received an intravenous injection of 0.5 ml. per kilogram (not more than 5 ml. total) of 10 per cent calcium gluconate diluted to a 3 per cent solution to compensate for diffusion of calcium into the dialyzing fluid. In Patient 4 calcium administration was inadvertently omitted and a mild state of tetany occurred which responded promptly to therapy.

CHEMICAL ANALYSES

Heparinized plasma, peritoneal fluid, and urine were analyzed for salicylate by a micromodification of Brodie's[3] method; sodium

*Albumisol was supplied by Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, Pa.

The electrolyte content of the diluent is as follows:

Na+	142.0 mEq./L.
Ca++	0.6 mEq./L.
Cl−	130.0 mEq./L.
Acetyltryptophanate	4 mM./L.
Caprylate	4 mM./L.

Potassium, as KCL, in an amount of 5.0 mEq./L. was added.

Table II. Quantity of salicylate removed from the body by dialysis and by urinary excretion (plasma volume = 5 per cent body weight)

Patient	Calculated plasma volume (ml.)	Number of dialyses	Volume of dialysis fluid (per kilogram per dialysis) (ml.)	Calculated circulating salicylate		Calculated salicylate removed from plasma (mg.)	Total urinary excretion during dialysis (mg.)	Total salicylate removed by dialysis (mg.)	Total salicylate removed from body (mg.)	Salicylate removed from extravascular space	
				Predialysis (mg.)	Postdialysis (mg.)					(mg.)	(%)
1	500	2	50	205	141	64	41.5	310	351.5	287.5	81.8
2	487	2	102.5	303	198	105	107.4	771	878.4	773.4	88.1
3	680	3	88	349	156	193	165	602	767	574	74.8
4	562	3	60	254	139	115	117.4	441	558.4	443.4	79.4
5	430	2	68	174	109	65	59.4	392.5	451.9	386.9	85.6
6	590	3	105	309	163	146	290.5	1,085	1,375.5	1,229.5	89.4
7	725	2	86	306	177	129	115.3	419	534.3	405.3	75.9

and potassium, by flame photometry; calcium, by EDTA titration; total protein, by the Biuret method; and osmolarity, with the use of the Fiske osmometer. Blood pH was determined with a Beckman microelectrode submerged in a constant temperature water bath maintained at 37° C. Carbon dioxide content was determined by the standard gasometric method of Van Slyke or by use of the Fisher clinical gas partitioner.*

In order to gain information concerning the rate of diffusion of salicylate into the dialyzing fluid and the exchange of ions, analyses were conducted at more frequent intervals than would be necessary or practical from a purely clinical point of view.

RESULTS AND DISCUSSION

The salicylate levels in plasma, prior to and during the lavage, and in lavage fluid during the dialysis periods, are shown in Tables I and II and illustrated in Fig. 1. The plasma levels prior to dialysis ranged from 40.4 to 62.3 mg. per cent. As had been observed by others,[4-9] the level of salicylate in the plasma was not an adequate measure of the degree of clinical toxicity. The most severely ill patients were Cases 3, 4, and 6, whose respective plasma levels were 51.3, 45.2, and 52.3 mg. per cent; Case 2, with the highest level in this series, 62.3 mg. per cent, appeared less toxic.

If the toxicity of salicylate is a function of its extravascular level (presumably the tissue concentration) then the efficacy of a method of treatment, which involves the clearance of salicylate from the body, is proportional to its ability to extract salicylate from the tissues. The concentration of salicylate in the dialysis fluid increased steadily during the 3-hour lavage period and the concentration approached or equaled that of plasma in the majority of instances (Fig. 1). Within the time limits of the lavage periods used in this study, achievement of salicylate equilibration between lavage fluid and plasma did not seem related to the quantity of dialysis fluid introduced into the peritoneal cavity. In Patients 1, 2, 5, and 6 in whom a high degree of equilibration occurred, the volume of dialysis fluid ranged from 50 to 105 ml. per kilogram per dialysis; in Patients 3, 4, and 7 equilibration was less striking and the volume of dialysis fluid ranged from 60 ml. to 88 ml. per kilogram per dialysis. If binding to albumin is an important factor in achieving equilibration and in removing salicylate, the quantities of albumin present, even with the use of smaller volumes of Albumisol, seemed sufficient for this purpose.

Assuming plasma volume equals 5 per cent of body weight and (a) utilizing changes in plasma salicylate during the

*Manufactured by Fisher Scientific Company, Pittsburgh, Pa. This instrument separates and measures gases contained in liquid samples by means of gas chromatography.

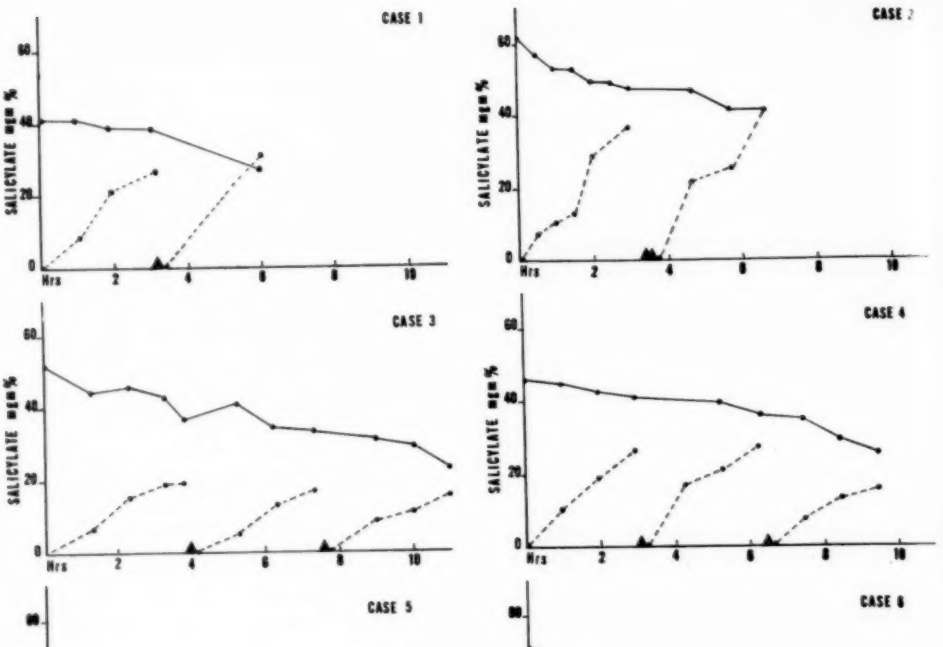

Fig. 1. Salicylate levels in plasma and peritoneal fluid during lavage periods.

dialysis periods, (b) measuring salicylate removed by dialysis, (c) measuring urinary excretion of salicylate, and (d) combining b and c as a measure of total salicylate cleared from the body, we find by calculation that 75 to 90 per cent of the salicylate eliminated came from extravascular fluids (Table II). Moreover, comparison of the amount of salicylate removed by dialysis with that excreted in the urine (Table II) illustrates that much greater quantities of salicylate were eliminated by dialysis. Therefore, most of the salicylate removed by dialysis must have come from the extravascular spaces.

A comparison of salicylate levels in plasma and dialysis fluid obtained in this study with those obtained in our animal studies[1] points out a slightly greater tendency in the latter for achievement of equilibration and in some instances for levels in the dialysis fluid to exceed those present in plasma. We have no explanation for this difference. Data concerning the quantities of protein-bound and diffusible salicylate in the various fluid compartments of the body and in the dialyzing fluid would be useful in this respect. In the animal studies toxicity was produced rapidly by intravenous administration of sodium salicylate. In contrast, patients included in this study ingested acetylsalicylic acid 6 to 24 hours prior to hospitalization (see case summaries). Equilibration of salicylate in plasma and dialysis fluid occurred or was approximated in Cases 1, 2, and 5 (and Case 6 to whom sodium bicarbonate was administered) after 11, 9½, 11, and 24 hours, respectively, had elapsed following ingestion of salicylate and before admission to the hospital. In Cases 3, 4, and 7 equilibration was less satisfactorily attained; the time of ingestion of aspirin was 13½, 24, and 6 hours, respectively, prior to entering the hospital. Thus, the length of time between acetylsalicylic acid ingestion and hospitalization was similar in these two groups and did not seem to influence the degree of salicylate equilibration attained between plasma and dialyzing fluid.

With the exception of Patient 2, plasma salicylate concentrations decreased slowly to levels below 30 mg. per cent during the second or third lavage which corresponded to 4 to 8 hours after initiation of the first lavage. However, the rate of decrease in plasma salicylate concentrations was not proportional to total quantity of salicylate removed by dialysis (Tables I and II, Fig. 1).

As anticipated, the total quantity of salicylate removed was proportional to the number of dialyses performed and to the volume of fluid, and hence the total quantity of albumin, used. The greatest total quantity of salicylate was removed in Patient 6. In this case, 3 dialyses of 105 ml. per kilogram per dialysis resulted in the removal of 1,085 mg. of salicylate. In Patient 1, in whom good equilibration between plasma and dialysis fluid occurred, 2 dialyses of 50 ml. per kilogram per dialysis resulted in the removal of 310 mg. of salicylate. In Patient 2 two lavages with 102.5 ml. per kilogram per dialysis removed 770.8 mg. and presumably performance of a third dialysis in this patient would have resulted in removal of additional salicylate. The clinical improvement in this case influenced our decision to use 2 dialyses rather than 3, despite a plasma salicylate level of 41 mg. per cent at the end of the second period.

As a result of the foregoing observation, it is our opinion that 85 to 100 ml. of Albumisol per kilogram per dialysis is usually the optimal volume to be used when treating salicylate intoxication by this method. However, larger volumes may be used if tolerated. A total of three dialysis periods of 3 hours each is usually necessary. No contraindications exist to use of a greater number of dialysis periods if the clinical status and/or blood levels so indicate.

As previously mentioned, minimal effort was made to promote urinary excretion of salicylate. The greatest urinary excretion was obtained in Patient 6 to whom sodium bicarbonate was given on 2 occasions during the dialysis procedure in a quantity calculated to raise the plasma HCO_3^- 5 mEq. per liter. The pH of the urine remained at 5 to 5.5. This suggests the possible value of combining parenteral alkali administration (in states of acidemia) with intermittent peritoneal dialysis. Investigation of the influence of sodium bicarbonate administration on the diffusion of salicylate into the peritoneal dialyzing fluid is suggested by this result and at present is under way. Previous studies by others[10-18] have adequately demonstrated augmentation of urinary excretion of salicylate by administration of sodium bicarbonate.

Presumably intoxication is caused by the presence of elevated salicylate concentrations in the tissue and removal of large quantities of extravascular salicylate implies that these tissue levels are being effectively re-

Table III. Pre- and postdialysis electrolytes, osmolarity, and pH in plasma and dialyzing fluids

		Sodium (mEq./L.)		*Potassium (mEq./L.)*		*Calcium (mEq./L*	
		Pre	*Post*	*Pre*	*Post*	*Pre*	*Post*
Plasma	Range	128-144	127-154	2.8-5.2	3.2-5.0	5.1-7.2	0-6.8
	Average	135	136	3.9	4.1	5.9	5.1
Dialysis fluids	Range	—	126-159*	—	3.2-5.9*	—	1-6.7*
	Average	142	137	5.3	4.0	0.6	4.7

*Concentrations in final dialysis fluids.

duced. This assumption receives support from the correlation between the calculated extravascular salicylate removed and the clinical improvement observed in these cases. Moderate improvement in the sensorium was most dramatic early, occurred usually by the end of 3 hours and progressed rapidly thereafter. The Kussmaul breathing pattern was slower to improve. This is not surprising in view of the well-known stimulating effect of salicylate upon the respiratory center, as well as the metabolic acidosis associated with its toxicity. More generous use of alkali in the presence of existing acidemia seems indicated because it may favorably influence but not necessarily correct the respiratory pattern and because it influences the removal of salicylate from the body.

It will be noted in Table III that acidemia was not corrected in these patients at the end of the dialysis periods, though the salicylate levels had been significantly reduced. It will be recalled, however, with the exception of Case 6, that we intentionally made no particular attempt to correct acidemia or promote excretion of salicyalte because of the desire to evaluate intermittent peritoneal dialysis per se as a method of eliminating salicylate from the body. In this case, in which alkali was used, the serum HCO_3^- rose in 10 hours from 9 to 16 mEq. per liter. The chloride content of Albumisol is 130 mEq. per liter and may have had an influence in perpetuating an acidosis. There was a slight decrease in chloride levels of Albumisol while in the peritoneal cavity but there was no significant increase in serum chloride level in any case.

Reference to Table III, along with uniform presence of an acid urine (pH5), demonstrates that salicylate intoxication resulted in metabolic acidosis in these patients at the time of admission to the hospital. Moderate hyponatremia and hypokalemia were frequently present also. The serum calcium concentrations and plasma osmolarity were normal. The combination of normal serum osmolarity and hyponatremia suggests modest elevation of nonionized solute concentrations such as urea. Addition of K^+ to the Albumisol and routine administration of calcium gluconate intravenously, combined with a regimen of parenteral fluid therapy dependent largely upon homeostatic mechanisms for specific ionic repair, seemed to prevent undesirable alterations in plasma levels of Na, K, Ca, and osmolarity. As anticipated, the ionic concentrations and osmolarity of the dialysis fluid approximated those of the plasma.

SUMMARY AND CONCLUSIONS

We have demonstrated the effective removal of salicylate from patients with salicylism by means of intermittent peritoneal dialysis, using 5 per cent albumin in an isosmotic diluent (Albumisol). The results obtained in 7 patients thus treated were similar to those obtained in a previously reported experimental study in dogs.

The procedure was well tolerated and no complications ensued. Varying volumes of dialyzing fluid ranging from 50 c.c. per kilogram per dialysis to 105 c.c. per kilogram per dialysis were evaluated in this study and 2 or 3 dialysis periods of 3 hours each were carried out in each patient. Good equilibration of salicylate between plasma and peritoneal

Bicarbonate (mEq./L.)		pH		Osmolarity (mOs./L.)	
Pre	Post	Pre	Post	Pre	Post
9.6-15.4	10.2-18.2	7.2-7.4	7.33-7.52	275-300	271-330
12.8	14.0	7.3	7.43	286	288
—	4.6-16.4*	—	—	—	237-292*
0	12.0	—	—	277	268

neal fluid occurred and could not be related to the volume of fluid per se. The total quantity of salicylate removed from the body, however, was proportional to the number of dialyses and the volume of fluid used which is related to the quantity of albumin introduced into the peritoneal cavity. It is recommended that 100 c.c. of Albumisol per kilogram per dialysis be used for 3 consecutive dialyses. There is no contraindication to the use of larger volumes of dialyzing fluid, if tolerated, or to a greater number of dialyses, if indicated.

In view of a frequent hypokalemia and a diffusion of potassium and calcium into the dialyzing fluid it is essential to add 5 mEq. per liter of potassium to the dialyzing fluid and to administer calcium gluconate intravenously during the period of dialysis.

Fluid therapy remains to be an important consideration and potassium, sodium chloride, sodium bicarbonate, glucose, and water in adequate quantities is also recommended in the management of salicylate intoxication. Sodium bicarbonate in one case, in addition to promoting urinary excretion of salicylate, may have influenced its diffusion into the dialyzing fluid; however, additional confirmatory studies are required concerning this point.

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The effect of high caloric feeding on the growth of premature infants

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THIS study was undertaken to determine whether the rate of growth of premature infants could be accelerated by increasing the caloric intake. Hardy and Goldstein[1] found that ad libitum feeding of premature infants did result in a greater weight gain. It is interesting to note that they obtained increased weight gain when intake was increased from 125 to between 140 and 150 calories per kilogram; however, further increase in calories did not produce a still greater gain in weight. These studies are complicated by the fact that caloric increase was accomplished by feeding larger volumes of the same formula with the result that electrolyte intake was also increased; this is also a factor that might have influenced the amount and character of the weight gain.[2] Keitel and his co-workers[3] noted that the spontaneous intake of the premature infant was limited by the volume of the feeding rather than its caloric content. Using a concentrated humanized type of infant feeding, they were able to increase caloric intake substantially. Markedly improved weight gains were reported and they gained the impression that growth in length also was increased. This present study was designed to investigate the influence of increased caloric density on weight gain and linear growth.

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METHODS

Linear growth was determined by the method of Day and Silverman.[4] This measures the growth of the fibula as recorded on a roentgenogram, taken by a standard technique. The fibula is measured by placing calipers at the diagonally opposite ends of the bone and then placing the calipers on a millimeter rule. We attempted to reduce technical errors as much as possible by having all films taken by the same technician using the same target distance and exposure; two films of both the left and right fibula were taken. Both diagonals were measured twice on each film. To reduce personal errors in measuring, each time a measurement was taken, the calipers were opened wide and then brought closer together until they exactly contacted the corners of the fibula. Thus, each length that is recorded represents the average of four measurements.

High caloric intake was provided by the

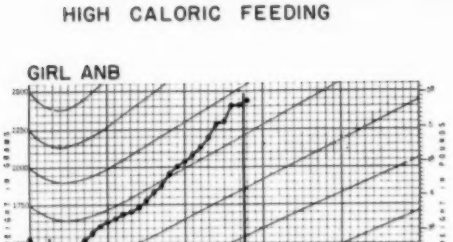

Fig. 1. Effect of high caloric feeding on weight curve of Baby Anb.

use of a humanized type of prepared infant formula.* The preparation was used straight from the can, and thus provided a feeding which was twice as concentrated as that usually recommended. This feeding contained 1.3 calories per milliliter. Ten infants who received this feeding had serial x-rays of the fibula. Each of these had two sets of films separated by an interval of 7 to 20 days, and a third set of films was taken in 2 of these cases. Birth weights of these infants varied between 1,120 and 2,040 grams, and they were between 4 and 29 days of age when the first x-rays were taken.

The controls were premature infants who were in the nursery at the same time and whose care was exactly the same except for the feeding, which was less concentrated†; 1 ml. provided 0.9 calorie. They received 120 to 130 calories per kilogram and 5.5 to 6.0 grams of protein per kilogram. There were 11 infants in this group whose birth weights ranged from 1,440 to 1,930 grams and they were 3 to 23 days old at the time the first film was taken. Three of these infants had three sets of films, while the remainder had two sets.

*Similac liquid.
†Olac.

The weight gain of all infants was plotted on the weight graph used routinely in our premature unit.[5]

RESULTS

It was not possible to feed any of these infants double the usual caloric intake because of their refusal to take an equivalent volume of the double-strength formula. However, all the test babies received 155 to 180 calories per kilogram after they reached 10 days of age, which provided 4.75 to 5.1 Gm. of protein per kilogram. This resulted in extremely good gain in weight and the weight curves of most of these babies rose to the next higher channel on the weight grid. Such a weight curve is illustrated in Fig. 1. The rate of weight gain for the infants fed the high caloric feeding and the usual feeding is recorded in Table I.

This increased weight gain was obvious clinically. The babies all appeared plump and had unusually rounded cheeks for premature infants. They reached discharge weight at an earlier age. The routine discharge weight was attained 5 to 21 days earlier than that of infants receiving the usual caloric intake. The smaller infants who received the high caloric feeding for the longest period of time had their hospital stay shortened the most.

There were no differences in growth rate of the fibula between the two groups of infants. In the control group the average rate

Table I. Weight gain

Control babies		*Babies fed high caloric formula*	
Baby	*Grams/day*	*Baby*	*Grams/day*
Fe	20.5	Lo A	40
Su A	24.8	Lo B	38
Su B	18.5	Wo	40
Ko	29	Anb	50
Hi	43	Ang	38.5
Wa	35	Ch	36.5
Je	26	Do	50
Mi	30	Gu	50
Mo A	24	Th	48
Mo B	20	Al	39.5
Or	25		
Average	26.7	Average	43.9

Table II. Babies on high caloric feeding

Baby	Birth weight (grams)	First x-ray		Second x-ray		Fibula growth		Third x-ray		Fibula growth	
		Age (days)	Weight (grams)	Age (days)	Weight (grams)	Left (mm./day)	Right (mm./day)	Age (days)	Weight (grams)	Left (mm./day)	Right (mm./day)
Lo A	1,700	5	1,710	25	2,580	0.24	0.21				
Lo B	1,870	5	1,800	18	2,430	0.19	0.11				
Wo	1,950	4	1,900	11	2,300	0.16	0.20				
Anb	1,170	17	1,370	38	1,870	0.27	0.24	52	2,550	0.14	0.15
Ang	1,530	10	1,630	24	2,280	0.21	0.22				
Ch	1,900	11	1,970	18	2,270	0.18	0.21	25	2,450	0.17	0.22
Do	2,040	8	2,100	15	2,530	0.28	0.26				
Gu	1,550	14	1,900	21	2,330	0.30	0.24				
Th	1,470	26	1,870	33	2,350	0.16	0.17				
Al	1,120	29	1,730	43	2,100	0.13	0.13				
Average growth											
Left fibula		0.20									
Right fibula		0.18									

Table III. Control babies

Baby	Birth weight (grams)	First x-ray		Second x-ray		Fibula growth		Third x-ray		Fibula growth	
		Age (days)	Weight (grams)	Age (days)	Weight (grams)	Left (mm./day)	Right (mm./day)	Age (days)	Weight (grams)	Left (mm./day)	Right (mm./day)
Fe	1,620	7	1,620	21	1,900	0.18	0.19	28	2,150	0.16	0.19
Su A	1,660	19	1,810	26	2,050	0.30	0.24	40	2,330	0.16	0.18
Su B	1,440	19	1,870	26	2,000	0.21	0.27	40	2,260	0.16	0.16
Ko	1,460	23	1,710	38	2,150	0.12	0.10				
Hi	1,540	15	1,650	29	2,250	0.26	0.21				
Wa	1,537	8	1,600	22	2,160	0.23	0.25				
Je	1,360	22	1,720	29	1,900	0.23	0.23				
Mi	1,750	3	1,680	14	2,070	0.16	0.17				
Mo A	1,530	8	1,540	21	1,850	0.22	0.19				
Mo B	1,930	8	1,840	21	2,200	0.25	0.25				
Or	1,900	5	1,800	19	2,150	0.17	0.13				
Average growth											
Left fibula		0.20									
Right fibula		0.20									

of growth of both the left and right fibulas was 0.20 mm. per day. In the high caloric group the average rate of growth of the left fibula was 0.20 mm. per day and of the right fibula 0.18 mm. per day. There were differences in individual rates of growth which varied from 0.10 to 0.30 mm. per day. The majority of measurements were distributed about 0.20 mm. per day. It was not possible to relate these different growth rates to either the birth weight, the weight at which the measurements were taken, or the age when the measurements were taken. All the growth data are recorded in Tables II and III.

DISCUSSION

These data demonstrated that an accelerated gain in weight in premature infants can be brought about by an increase in caloric intake. The composition of this added weight should be examined. We do not believe it represents fluid retention since the electrolyte content of both formulas was very similar. The failure to influence linear growth, in addition to the fact that the protein content of the high caloric feeding was somewhat lower than that of the control feeding, suggests that this weight is not due to the deposition of new protein-rich tissue. Also, nitrogen retention studies performed

on 3 other infants given the high caloric feeding who were not included in this study reveal nitrogen retention of the same order of magnitude as that obtained with the control feedings. It appears, by elimination, that this weight gain is due to fat deposition, and this impression is strengthened by the appearance of these infants.

The advantage of accelerating gain in weight and thereby shortening the hospital stay of premature infants is open to some question. This may result in the discharge of physiologically immature infants who simply weigh more. The wisdom of earlier discharge of premature infants cannot be ascertained until more critical methods of evaluating the degree of maturity are developed.

SUMMARY

A high caloric feeding in the form of a concentrated humanized type of prepared infant formula was given to 10 premature infants. It resulted in an increased rate of gain in weight. However, linear growth as measured by the increase in rate of growth of the fibula was not affected by this feeding.

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Sleep patterns of the newborn

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THE normal waking and sleeping patterns of newborn infants are of theoretical as well as practical interest. The relationships between the nonspecific reticular activating system of the brain stem and the cerebral cortex have become of major importance in recent discussions of arousal mechanisms. The experimental aspects of this subject have been extensively reviewed recently by Magoun[1] and others.[2, 3] The human infant presents us with an opportunity to study in normal subjects some neurological functioning with perhaps a minimum of cortical interference. Since it is now believed by many that the brain stem plays a very important function in the waking and sleeping states, it seems appropriate to study sleep and arousal in the newborn infant. Although such a complex problem warrants refined studies with modern instrumentation, nevertheless, a clinical, descriptive study is not inappropriate as a point of departure.

From a practical point of view, descriptive information of the usual sleep patterns of newborn infants can be useful to doctors and nurses alike. This information may be of help in interpreting normal behavior of the newborn infant to the uninitiated mother or in establishing hospital procedures for the newborn.

There are no reports of large numbers of newborn infants studied from the point of view of sleep patterns. This is perhaps related to the fact that in most hospitals babies are awakened for feedings at regular intervals during the neonatal periods. Thus, any 24-hour study of the spontaneous, uninterrupted sleep patterns is precluded.

There are a few studies of single cases or of a small number of cases such as those of Simsarian and McLendon,[4] Gesell and Amatruda,[5] Bühler and Hetzer,[6] and Hellbrügge, Lange, and Rutenfranz.[7] The latter authors have extensively reviewed the literature.

Hellbrügge and co-workers[7] indicate 5 modern European textbooks of pediatrics that report that the newborn baby sleeps 19 to 22 hours out of the 24-hour day and they trace this same statement back through numerous textbooks of the past 50 years. Kleitman and Engelmann[8] also found statements in the literature that infants in the first week of life are awake only about 2 hours out of 24. Kleitman and Engelmann,[8] as do Hellbrügge and colleagues,[7] point out that this information about the sleeping and waking patterns of the newborn is in conflict with some existing reports of the continuous observations of infant sleep.

Gesell and Amatruda[5] found that one newborn infant observed continuously slept ap-

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proximately 60 per cent of the time on the third day (14.4 hours), 875 minutes or 14.5 hours on the fourth day, and 14.04 hours on the sixth day. Simsarian and MacLendon,[4] by use of continuous observation records of one child found that he slept an average of 16.5 hours per day during the first 2 weeks of life. Hellbrügge and colleagues,[7] by observing the percentage of babies awake every other hour in a nursery for newborn infants, concluded that newborn babies are far more wakeful than was commonly reported and agreed with the studies quoted above. On the other hand, Bühler and Hetzer[6] observed 5 newborn babies continuously and found that in the first 10 days the average sleeping time was 80 per cent of the day or about 19 hours per day. It is possible that the differences in these reports result from the individual variations of the infants studied.

Kleitman and Engelmann[8] in a very thorough study of continuous sleep-wake records of 19 infants from 3 to 26 weeks of age found that at 3 weeks of age the average sleeping time was 14.86 hours with no change in the total sleeping time during the subsequent 12 weeks of life. By inference it is suggested that during the first 3 weeks of life the sleeping time of infants may be of this same magnitude.

This study was planned to evaluate some of these conflicting statements regarding the sleeping patterns of the newborn.

Table I. The total number of newborn infants examined and their distribution according to sex and type of feeding

	Breast fed	*Bottle fed*	*Total No.*	*Per cent*
Male	17	17	34	45.3
Female	26	15	41	54.7
Total no.	43	32	75	
Per cent	57.3	42.7		100

Table II. Summary of the average number of hours of sleep, the average longest sleep period, and the average number of feedings for each day for all of the infants studied (Total number 75)

	First day	*Second day*	*Third day*
Average number of hours of sleep	17.0	16.5	16.3
Average length of longest sleep period	4.9	4.3	4.2
Average number of feedings	4.9	6.0	6.2

MATERIAL AND METHODS

In the early part of 1958, one hundred successive mothers delivered at the Medical Center of the University of California at Los Angeles were asked to keep a behavior-day record of their babies' behavior in sleeping, waking, feeding, and crying. These records were kept on forms developed by Gesell and Ilg.[9] These forms have horizontal lines representing the days of age and vertical lines representing the 24 hours of the day, spaced ½ inch apart.

Each mother was instructed to draw a heavy, straight, pencil line horizontally across the number of hours the baby slept and indicate any portion of an hour as accurately as possible, and leave the area blank when the baby was awake. Feedings were indicated by the notation of Bt. for bottle and Br. for breast. Crying was indicated by a saw-toothed black line. The sleep periods were to be estimated as accurately as possible. The mothers were not given any instruction as to criteria for judging when the baby was asleep or awake. Each mother used her own criteria. The mothers seemed to be very sensitive to their own babies' activities.

When the babies were not with their mothers, the nurses were instructed to indicate to the mother or on the record directly, the babies' sleeping, waking, and feeding periods in the nursery. This tended to introduce some inaccuracies, although all feedings and times of feedings in the nursery were recorded. Since the babies were on self-demand feeding schedules, a few of the sleep and wake periods of babies in the nursery were gained by inference from the feeding times.

The inadequate records of mothers who did not bother to keep up the charts or of babies who spent much time in the nursery away from their mothers were discarded.

Table III. A comparison of the babies with the shortest total sleeping time on the first day (first quartile), Group A, and the longest total sleeping time on the first day (fourth quartile), Group B, relative to total duration of sleep on the subsequent days and their longest single period on all 3 days

		First	*Second*	*Third*	*First*	*Second*	*Third*
Group A	1	*10.8**	15.0	15.5	2.8	4.0	*6.0*
	2	12.3	16.0	15.1	4.4	3.8	*2.8*
(First quartile	3	12.8	15.5	15.0	4.4	2.9	3.8
for first day's	4	13.0	14.8	14.0	4.0	3.5	4.5
total sleep.)	5	13.5	*17.6*	17.0	*5.8*	4.1	4.5
	6	13.9	16.0	16.6	3.5	4.5	3.3
	7	14.0	16.3	16.8	4.4	3.8	4.9
	8	14.0	14.3	*12.5*	3.9	*2.8*	3.0
	9	14.0	13.8	17.0	2.8	3.3	5.8
	10	14.4	14.6	18.4	4.4	3.5	3.5
	11	14.5	15.3	18.3	3.1	*6.4*	4.6
	12	14.5	*10.5*	15.3	*2.1*	3.1	3.4
	13	14.6	16.1	*19.4*	3.9	3.3	3.6
	14	14.6	14.5	17.0	3.5	4.3	3.4
	15	14.8	11.0	16.0	3.5	3.6	4.5
	16	15.0	18.1	17.9	3.4	3.5	3.0
	17	15.1	13.3	15.0	4.3	3.0	3.8
	18	15.3	17.4	17.6	3.8	6.0	4.3
	19	*15.4*	15.1	14.1	4.1	3.0	3.5
Average		14.04	15.00	15.71	3.88	3.88	3.95
Group B	57	*18.3*	*13.5*	16.0	*3.8*	4.3	5.5
	58	18.5	18.0	19.0	3.9	4.3	4.8
(Fourth quartile	59	18.6	15.0	13.0	5.0	4.5	*2.8*
for first day's	60	18.6	14.6	15.0	5.4	4.1	4.6
total sleep.)	61	18.8	14.0	16.5	5.8	4.0	5.3
	62	18.8	18.6	14.8	7.5	*7.6*	*6.8*
	63	19.3	21.0	17.8	5.9	8.5	3.6
	64	19.4	16.9	19.0	6.9	*3.4*	4.4
	65	19.6	17.5	17.4	5.4	3.6	2.8
	66	19.6	14.0	*11.0*	4.6	4.5	3.3
	67	19.6	15.0	14.0	9.5	5.9	3.1
	68	20.0	19.1	18.0	6.1	3.4	4.1
	69	20.1	17.9	16.6	6.5	5.5	4.9
	70	20.2	18.9	17.0	6.0	3.5	4.5
	71	20.9	16.0	17.8	5.4	4.8	4.8
	72	21.0	18.6	20.0	7.0	3.9	3.9
	73	21.0	18.0	19.5	*10.0*	2.3	4.3
	74	21.0	23.0	18.8	6.6	4.1	5.8
	75	*21.0*	*23.0*	*20.0*	5.4	6.6	5.0
Average		19.7	17.5	16.9	6.2	4.67	4.43

*The longest and shortest total duration of sleep per day and the longest and shortest single sleep period for each day are underlined.

Since most of the mothers were discharged on the fourth day not counting the day of delivery, only 3 complete days from midnight to midnight are recorded. For the purposes of this study the first day is the first complete period from midnight to midnight and the second and third days are similarly defined.

The results of this study are based on the analysis of these 3 hospital days of the newborn infant.

RESULTS

Satisfactory charts were obtained on 75 babies. Of these, there were 26 females and 17 males who were breast fed and 15 females and 17 males who were bottle fed. Thus

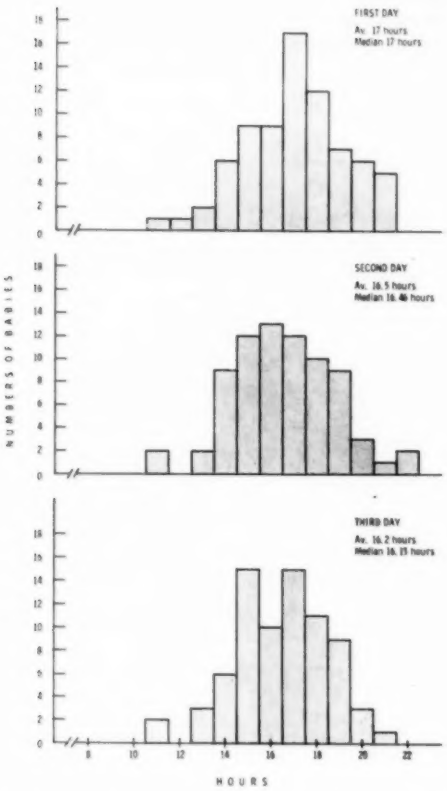

Fig. 1. The distribution of the total duration of sleep for each of the 75 newborn infants for each day.

there were a total of 41 female and 34 male infants of whom 43 were breast fed and 32 bottle fed (Table I).

The average total sleeping time for all the babies was 17 hours the first day, 16.5 hours the second day, and 16.2 hours the third day. The average longest sleeping period for all of the babies was 4.8 hours the first day, 4.2 hours the second day, and 4.5 hours the third day. The average number of feedings for all of the babies was 4.9 on the first day, 6.0 on the second, and 6.2 on the third (Table II).

The longest uninterrupted sleep period for all 3 days occurred on the first day for 53.3 per cent of the babies, on the second day for 24 per cent, and on the third day for 22.7 per cent. When the 24-hour day was divided into three 8-hour periods, it was found that 24 per cent of the babies had their longest sleep period of the 3 days between 7 A.M. and 3 P.M., 18 per cent between 3 P.M. and 11 P.M., and 57 per cent between 11 P.M. and 7 A.M.

The distribution of the total sleeping time of the 75 babies was as follows. The range on the first day was from 10.8 hours to 21 hours of total sleep with the mean, median, and mode of the distribution all at 17 hours. On the second day the distribution was a little greater with the range from 10.5 hours to 23 hours and a mean of 16.5 hours, a

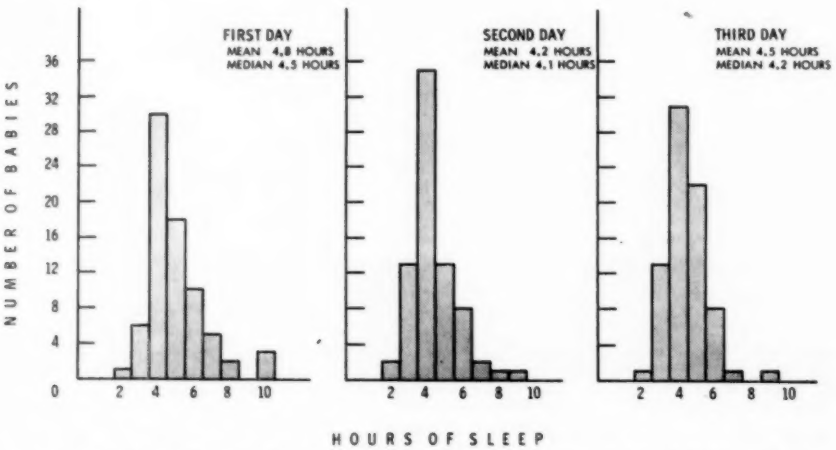

Fig. 2. The distribution of the longest single period for each of the 75 babies each day.

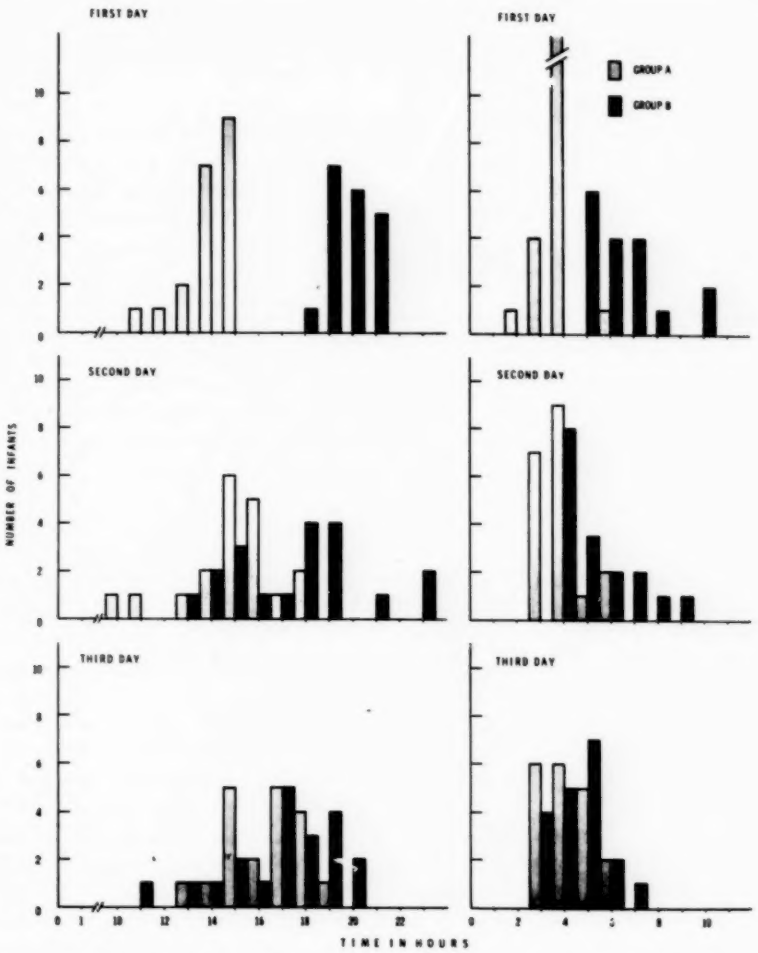

Fig. 3. The distribution of the total duration of sleep per day, on the left, and the longest sleep period per day on the right, for the babies in Group A (shaded) and the babies in Group B (black).

median of 16.4 hours, and a mode of 15 hours. The distribution for the third day was from 11.4 hours to 21 hours with a mean of 16.2 hours, a median of 16.5 hours, and a mode of 17 hours (Fig. 1). While there appears to be a tendency for the babies to sleep a somewhat shorter length of time on the second and third days, the 3 days seem to be generally comparable.

The longest single period of sleep on the first day ranged from 2.1 hours to 10.0 hours with a mean of 4.8 hours, median of 4.5 hours, and mode of 4 hours. The second day is similar but the range is narrower with a distribution from 2.3 hours to 8.5 hours and a mean of 4.2 hours, median of 4.1 hours, and mode of 4 hours. The third day is essentially the same with a range of 23 hours to 8.80 hours and a mean of 4.5 hours, median of 4.2 hours, and mode of 4 hours (Fig. 2).

In order to evaluate the persistence of sleeping patterns of individual babies through all 3 days, the records of the babies were arranged in sequential order relative to the

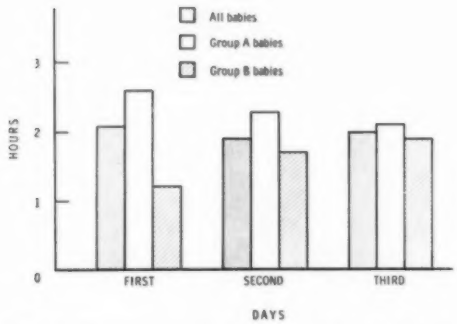

Fig. 4. The average longest wakeful period each day for all babies and Group A and Group B babies.

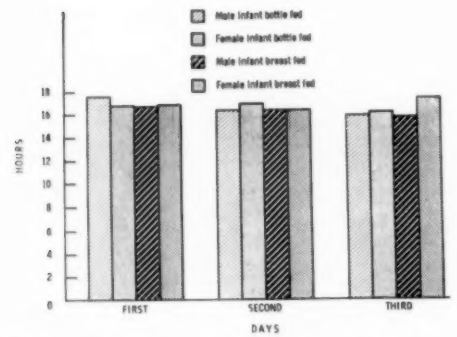

Fig. 5. The average total hours of sleep per day according to the sex of the infant and type of feeding.

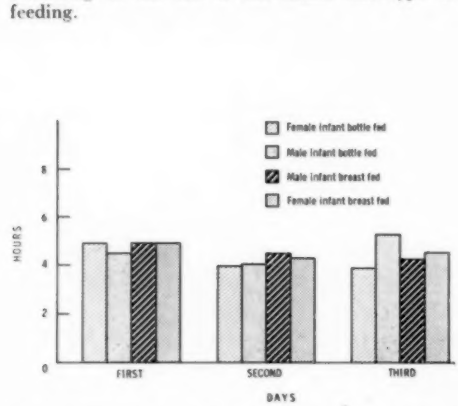

Fig. 6. Average longest sleep period per day. The distribution of the feedings for each day according to the sex of the infant and the type of feeding. Each infant is represented by the symbols as indicated.

total duration of their sleeping time on the first day. The baby with the shortest total sleeping time on the first day was placed first and thus the baby with the longest sleeping time on the first day was last. The first 19 babies or first quartile were designated as Group A and the last 19 babies or fourth quartile were designated as Group B.

The range of total sleeping time on the first day for the Group A infants was from 10.8 hours to 15.4 hours with a mean of 14.04. The range of total sleeping time for the babies in Group B on the same day was from 18.3 hours to 21.0 hours with a mean of 19.7 hours. Thus there was a major difference in total sleeping time on the first day between these two groups of babies (Table III, Fig. 3).

On the second day the babies of Group A persisted as "short" sleepers and the babies in Group B persisted as "long" sleepers but the difference was less. The babies in Group A had a mean total sleeping time of 15 hours with a range from 10.5 hours to 17.6 hours, while the babies in group B had a mean sleeping time of 17.5 hours with a range of 13.5 hours to 23 hours. By the third day there was complete overlapping of the range of sleeping times with a diminution in the difference between the means. The range of sleeping times for Group A was from 12.5 hours to 19.4 hours with a mean of 15.7 hours, and the range for Group B was from 11.0 hours to 20.0 hours and a mean sleeping time of 16.9 hours (Table III, Fig. 3).

The difference in total sleeping time between the Group A "short" sleepers and the Group B "long" sleepers could be the result of 2 types of sleeping patterns. The babies in both groups could have single sleep periods of similar duration with the babies in Group A having prolonged waking periods as the only cause of the difference in the total sleeping times. On the other hand, the babies in Group A could have a combination of shorter individual sleeping periods with more frequent prolonged waking. The latter appears to be the case. In Group A on the first day the mean duration of the longest

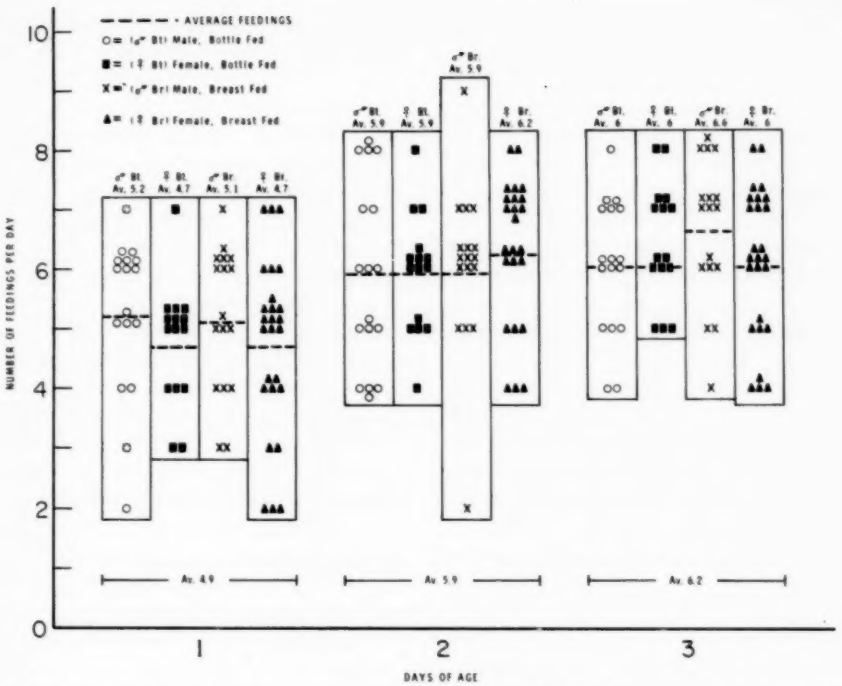

Fig. 7. The distribution, range, and average frequency of feedings for each day is presented according to the sex of the baby and type of feeding. Each infant is represented by a symbol as indicated.

single sleep period was 3.88 hours with a range from 2.8 hours to 5.8 hours. In Group B the mean duration of the longest single sleep period was 6.2 hours with a range of 3.8 hours to 10.0 hours. On the second day the difference was somewhat less and there was more overlapping of the range with the data as follows: Group A, mean 3.88 hours and range 2.8 hours to 6.4 hours, and Group B, mean 4.67 hours and a range of 3.4 hours to 7.6 hours. By the third day overlap of the range of duration of longest sleep period was complete and the means more comparable as follows: Group A, mean 3.95 hours and range 2.8 hours to 6.0 hours, and Group B, mean 4.43 hours and range 2.8 to 6.8 hours (Table III, Fig. 3).

The average longest wakeful period for all of the babies was 2.1 hours on the first day, 1.9 on the second, and 2.0 on the third. For Group A babies the average longest wakeful periods for the 3 days was 2.6, 2.3, 2.1, respectively, and for Group B 1.2, 1.7, and 1.9 (Fig. 4).

Neither the type of feedings the babies received nor their sex seemed to be a significant factor in the total number of hours of sleeping time, general pattern of longest single sleep period, or frequency of feedings (Figs. 5, 6, and 7).

The average number of feedings for the first day was 5 (4.9), the second day 6 (5.9), and the third day 6 (6.2). The range in frequency of feedings was from 2 to 7 on the first day, 2 to 9 on the second, and 4 to 8 on the third day (Fig. 6).

DISCUSSION

It is recognized that in this study the duration of the periods of sleep and wakefulness were not precisely determined. A baby could awaken briefly and if quiet fall back to sleep

again without the mother noticing the event. This would be most likely to happen at night when the mother was sleeping. It is perhaps for this reason that 57.4 per cent of the babies were recorded as having their longest single sleep period between 11 P.M. and 7 A.M. Despite the recognized inaccuracies inherent in allowing the babies' mothers to determine sleep and wakefulness and record them, the results are similar to the results of Simsarian and McLendon,[4] Gesell and Amatruda,[5] and Kleitman and Engelmann.[8]

In this study no attempt was made to correlate the sleep patterns with either the type of labor and delivery or the analgesia and anesthesia given the mother before and during delivery. These factors very probably influence the sleeping patterns of the newborn baby, especially on the first day. It may be for this reason that the babies in this study with the extreme sleeping patterns on the first day, Groups A and B, show a definite tendency by the third day to move toward the mean for all the babies.

Despite the inadequacies of recording in our study it seems apparent that newborn infants sleep less than the 19 to 22 hours per day often indicated in the literature quoted by Hellbrügge and associates,[7] and Kleitman and Engelmann.[8] The 75 infants observed in our study were awake 7 to 8 hours per day or 30 per cent to 35 per cent of the 24 hours and asleep 16 to 17 hours or 65 per cent to 70 per cent of the day. Neither the sleeping nor the waking periods were sustained for any long period of time.

The explanation for the periodicity of the alternate sleeping and waking periods is not known. There are many authors who feel that this is directly related to hunger. Irwin[10] measured the motility of newborn infants before and after feedings and found the activity high before feedings and very high during an 8-hour interval of enforced deprivation of feeding. Since he kept the environmental light, sound, and temperature constant, he felt the stimulus was of internal origin and probably from the gastrointestinal tract. Marquis[11] found newborn babies quieter on a 3-hour schedule of feedings than on a 4-hour schedule. On the other hand Richards[12] was unable to find any correlation between gastric motility and bodily movements. Gesell and Amatruda[5] and Aserinsky and Kleitman[13] agree that there may be internal stimuli causing periodic arousal but feel that this is not necessarily hunger or gastrointestinal motility. By careful observation and frequent photographic recording of one infant, Gesell and Amatruda found 38 distinguishable periods of sleep and wakefulness on the third day of life. Aserinsky and Kleitman[13] studied the actograms of sleeping infants ranging from 1 month to 7 months of age and correlated the activity cycles of these infants with their direct observations of the babies' eye movements. The eye movements tended to precede the general bodily movement of the infants and last a little longer. The eye movement activity and the general body activity occurred in periodically recurring cycles during the infants' sleep. These authors postulated that the infants would be most likely to awaken during one of these motility cycles. Therefore, the duration of any given sleep period would be that of a single motility cycle or some multiple of this. They determined the interval between motility cycles to be 60 minutes with some diurnal variations and some variations between infants. They attempted, with some success, to adapt this cycling to the reported self-demand feeding schedules and sleeping patterns of the infants in their own study and in those reported by Simsarian and McLendon[4] and Gesell and Amatruda.[5]

Wolff[14] has reported on the continuous 18-hour observations of 4 newborn infants. In this study all of the infants' activities during wakefulness and sleep were recorded. Of special interest is the fact that he observed "spontaneous" jerking or "startle" movements occurring at fairly regular intervals in infants in profound sleep. No external stimuli were visible as possible causes of these startles. When the infants were in a light sleep and exhibiting general bodily movements, "spontaneous startles" were less frequent. He concluded, "The occurrence and

periodic recurrence of spontaneous startles during some stretches of regular sleep point to an endogenous neural excitation."

Theoretically one might postulate as Aserinsky and Kleitman[13] have that the infant is subject to a cycling in the depth of his sleep manifest by periods of motility alternating with periods of immobility. This cycling may be determined by a central nervous system mechanism as yet unknown, independent of known exteroceptive and interoceptive stimuli. They concluded from their observations that one should not overlook "the possibility of an inherent rhythm within the C.N.S."

One may postulate that the infant awakes from sleep when the summation of the interoceptive and exteroceptive stimuli achieves a certain magnitude and impinges on him when he is in the most restless state of his sleep. These stimuli could be any combination of exteroceptive and interoceptive experiences such as proprioceptive feedback from the baby's own movements at a time when it is cold from a wet diaper, or has a full bladder, or when one or all of the above occur and in addition there is a sudden sharp noise in the room, or a passing truck causes marked vibration of the crib, etc. Hunger and gastrointestinal motility should not be completely neglected as participants in this summation of stimulation.

The nature of the cycling in sleep from motility to immotility is difficult to explain. Jouvet, Michel, and Courjon[15] have described a primitive sleep center in the reticular substance of the pons of the cat that has an internal, automatic periodicity of unknown origin.

It is possible that in newborn infants "primitive sleep" predominates with its automatic internal periodicity. Sustained sleep and wakefulness may be dependent on the more mature development of higher brain centers such as the cortex. This higher level organization of the central nervous system then would presumably supersede the more "primitive" periodic type of sleep. Certainly as infants mature in other neurological functions, characteristically sleep periods become longer[5-7] and conversely premature infants appear to have no periods of deep sleep.[5]

The electroencephalographic recording of wakefulness and sleep in full-term and premature infants as reported by Dreyfus-Brisac and co-workers[16] would tend to confirm this concept. The premature baby delivered after only 6 or 7 months' gestation does not show any differentiation between wakefulness and sleep in the electroencephalogram and the clinical differences are slight.[5] The premature infant of 8 months' gestation is somewhat more mature and in the electroencephalogram wakefulness and sleep tracings can be differentiated. It is interesting to note that the sleep tracing of premature infants of 8 months' gestation is like the wakeful tracing of the premature infant of 7 months' gestation. The full-term infant shows a more definite differentiation of wakefulness and sleep and by 3 months of age sleep spindles of the adult type can be found in the electroencephalographic tracing.

Future studies of the sleep of newborn and premature infants may contribute greatly to the ultimate understanding of some of the basic neurological principles of sleeping and waking states.

SUMMARY

The mothers of 75 full-term newborn infants recorded the sleeping and waking intervals of their infants during the first 3 days of life.

The average total duration of sleep on the first day was 17 hours, second day 16.5 hours, and third day 16.2 hours. The average longest sleep period on the first day was 4.8 hours, second day 4.2 hours, and third day 4.5 hours. The average number of feedings was 4.9 on the first day, 5.9 on the second, and 6.2 on the third. The sex of the baby or type of feeding received did not seem to influence the total duration of sleep per day, duration of longest sleep period, or number of feedings.

The babies with the shortest duration of total sleep on the first day tended to persist in their original pattern on the second day as did the babies with the longest total sleep

on the first day. However, by the third there was a shift to a common sleeping pattern for both groups.

The periodicity of the newborn baby's sleep may indicate the predominance of an unimpeded primitive sleep center, and the inability of higher cerebral activity to sustain prolonged periods of sleep and wakefulness.

Invaluable help in the collections of these records was given by all of the nursing staff of the Obstetrical Service of the Medical Center of the University of California at Los Angeles. We wish to thank in particular Miss Flanagan and Miss Darling for supervising the collection of the records.

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Congenital dextrocardia

Clinical, angiocardiographic, and autopsy studies on 50 patients

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CHICAGO, ILL.

(Concluded from the January issue.)

EMBRYOLOGY

The primitive cardiac tube is derived from 2 thin-walled mesodermic tubes at the caudal part of the headfold which by the second embryonic week fuses together at the midline into a single, elongated tube. The four-chambered tube grows much faster than the pericardial cavity in which it lies, and, as a result, it is compelled to bend. A spiralled S-shaped configuration is formed which resembles the normal sigmoid curve with the primary flexure on the right forming a U-shaped loop between the bulbus and ventricle. With further elongation of this tube, the bulboventricular loop grows caudally and ventrally while the sinus venosus is drawn out of the septum transversum and follows the atrium as it advances dorsally and cranially.[47]

If a contrasigmoid loop is formed during the initial bending of this tube, i.e., when the primary flexure is located to the left instead of the right, a Type I dextrocardia later develops.[48] De la Cruz and associates,[44] however, claim that inversion of the atria is not influenced by the direction of the bulboventricular loop since the 2 atria at this stage are "anchored" regions of the heart. They postulate that the final location of the anatomic right and left atrium depends upon their original location in the primitive tube. Type I dextrocardia, therefore, follows an initial inversion of the atria plus a contrasigmoid bending of the bulboventricular loop.

Nagel[49] explained the dextroversion as due to a developmental arrest of the heart at the sixth embryonic week, with the ventricular loop retaining its early rightward position and the heart occupying a median position almost symmetrically perpendicular to the long axis of the body. The heart fails to rotate leftward and instead rotates with its apex to the right accompanied by a slight degree of torsion of the vascular pedicle. Mesoversion may be explained similarly as a developmental arrest at about the sixth week where the median position of the heart persists because of its failure to rotate leftward as it normally should or rightward as it does in complete dextroversion. The necropsy findings and selective angiocardiograms of Case 25 (Fig. 8) illustrate this assumption since the position of the right and left freely communicating ventricular chambers at the midline, the absence of a distinct cardiac apex, and the position of the atrial chambers with a large interatrial communication are somewhat identical to

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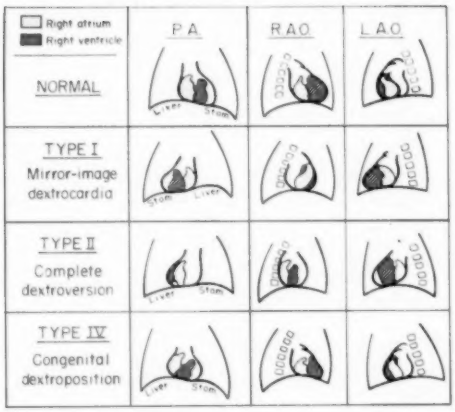

Fig. 11. Schema of the cardiac configurations and position of the right heart chambers in the conventional posteroanterior and anterior oblique chest roentgenograms in a normally placed heart, in mirror-image dextrocardia, in complete dextroversion and in congenital dextroposition. Note level of right diaphragm and position of liver and stomach in the various types.

the developing heart of a 4 to 9 mm. embryo.

Nagel's postulate does not explain the embryogenesis of mixed dextrocardia whereas the thesis of De la Cruz and co-workers[44] does. In mixed dextrocardia with atrial inversion (Type IIIa) the atria are inverted initially whereas the bulboventricular loop develops normally. Failure of the loop to swing to the left in later stages (as postulated in dextroversion) results in dextrocardia with atrial inversion and normally arranged ventricles. In the other type of mixed dextrocardia (Type IIIb), the atria are assumed to be normally situated in the heart tube initially, but a contrasigmoid bulboventricular loop is formed similar to that which occurs in Type I dextrocardia. Following the rightward swing of this loop, dextrocardia with ventricular inversion but with normally situated atria is produced.

Since Type IV dextrocardia is not a well-established entity, no embryologic thesis to explain its genesis has been presented. One may postulate that, after the median position of the embryonic heart is attained at about the sixth week, the normal leftward rotation along a vertical axis occurs but this is accompanied by an incomplete or insufficient leftward swing in the frontal plane so that the heart virtually remains in the midthorax.

Type V dextrocardia, unlike the preceding types, is not due to a developmental defect of the primitive cardiac tube per se, but is due to a mechanical displacement of the embryonic heart by any of its surrounding structures during later fetal life. The mode and extent of the displacement depend on the strength of the forces producing it. In simple dextroposition, the displacement consists of a rightward swing along the frontal plane only. With greater extracardiac force, the displacement occurs not only in the frontal plane but also in the horizontal plane, the anchored great vessels acting as a fulcrum. A pivotal rotation thus accompanies the initial dextroposition.

ROENTGENOLOGIC FINDINGS

The diagram in Fig. 11 illustrates the relative positions of the right heart chambers in the conventional posteroanterior, right anterior oblique, and left anterior oblique chest roentgenograms in a normally situated heart, in mirror-image dextrocardia, in complete dextroversion and in congenital dextroposition. The cardiac configuration in mirror-image dextrocardia, complete dextroversion, and mixed dextrocardia are similar in all respects. The apex is located laterally and to the right. In the right anterior oblique view, the cardiac silhouette resembles that of a normal left anterior oblique view, and vice versa. These findings are noted in complete dextrocardia regardless of the type. In mirror-image dextrocardia, however, the anterior chamber in the oblique views is the right ventricle while in complete dextroversion it is the left ventricle. The posterior cardiac border in the left anterior oblique view is formed by the left atrium in the former, whereas it is mostly formed by the right atrium in dextroversion. A right aortic arch is usually present in Type I dextrocardia but not in the

other types. The heart in mesoversion is at the midline and appears narrow in the frontal view but unusually wide in the lateral view. The interchanged cardiac configuration in the right and left anterior oblique views previously described in "complete" dextrocardia is also noted. There are no specific radiologic features in mixed dextrocardia.

It should be noted that in Types I, II, and III dextrocardia, the right hemidiaphragm is at a lower level than the left. This finding conforms with the concept[2, 14] that the normal upper level of the right diaphragm is not due to its elevation by the underlying liver but is due to the depression of the left diaphragm by the overlying heart. If it is caused by the "push" from the

Table IV. Salient electrocardiographic findings in various types of congenital dextrocardia

Case	Dextrocardia type	P				QRS				T	
		I	*aVR*	*aVL*	*aVF*	*I*	*aVR*	*aVL*	*aVF*	*I*	*aVL*
1	I	−	+	−	+	rSr′	RS	rSr′	qRs	−	−
2	I	−	+	−	+	rSR′	qR	Qr	rsR′	−	−
3	I	−	+	−	+	rS	qR	rS	rS	−	−
4	I	−	+	−	+	rSr′	qRs	rSr′	Rs	−	−
5	I	−	±	−	+	rSr′	rS	Qr	Rs	−	−
6	I	−	+	−	+	Qr	RS	Qr	Rs	−	−
7	I	−	iso.	−	+	QR	RSr′	QR	qrS	−	−
8	I	−	+	−	+	qR	rS	qR	Rs	−	−
9	I	−	+	−	+	qR	rS	qR	Rs	−	−
10	I	−	+	−	iso.	qR	rS	qR	Rs	−	−
11	I	−	+	+	−	QR	rS	QR	qR	−	−
13	IIa	−	±	−	+	QR	RS	Qr	qRS	−	−
14	IIa	+	−	+	+	QS	Rsr′	Qr	QRS	−	−
15	IIa	+	−	iso.	+	QS	rS	QS	qR	−	−
16	IIa	−	+	−	−	QR	RS	qR	rS	iso.	−
17	IIa	+	+	+	−	QS	Rs	QS	qrS	−	−
18	IIa	+	−	iso.	+	qrS	rsR′	QS	qRS	−	−
19	IIa	iso.	−	−	+	QR	rsR′	qR	rS	−	−
20	IIa	+	−	iso.	+	QR	RSr′	QR	qRs	−	−
21	IIa	±	±	±	iso.	QS	Rs	QRs	rSr′	−	−
22	IIb	+	−	+	iso.	qR	rS	qR	qR	±	±
23	IIb	+	−	−	+	qR	rS	QS	qR	iso.	−
24	IIb	−	+	iso.	±	RS	QR	rSr′	RS	−	−
25	IIb	+	−	−	+	qR	rS	QR	rsR′	iso.	−
26	IIb	+	−	+	+	Qr	RS	QS	QR	+	+
27	IIIa	−	+	±	−	Qr	qRs	Qr	rSr′	+	iso.
28	IIIb	iso.	−	−	+	QR	rS	QR	qR	−	−
29	IIIb	+	−	iso.	+	qR	rS	qR	qR	−	−
30	IIIb	±	−	−	+	Qr	rS	Qr	Rs	±	−
31	IV	+	−	iso.	+	qRs	rSr′	qrSr′	qRs	+	+
32	IV	+	−	+	+	qRs	rSr′	qRsr′	RS	+	+
33	IV	+	−	+	+	rS	rSr′	rS	qR	iso.	−
34	Va	+	−	±	+	RS	QR	qs	Rs	±	−
35	Va	+	−	+	+	Qrsr′	Rsr′	QRsr′	Qrs	+	+
36	Va	+	−	+	+	RS	QR	rS	qRs	+	+
37	Vb	+	−	iso.	+	QR	RS	QR	qR	+	iso.
38	Vb	+	−	+	+	QrS	RSR′	Qrs	qRS	+	+
39	Vb	+	−	−	qR	QRSr	RS	Qr	qRs	+	−
40	Vb	+	−	+	+	rS	QR	rS	qRS	±	−
45	Vb	+	−	+	+	QR	RS	Qr	QR	+	+
46	Vb	+	−	±	+	QR	RS	Qr	QR	+	+
47	Vc	+	−	+	+	QRs	RS	QR	qR	+	+
48	Vc	±	−	−	+	Qr	Rs	Qr	QR	+	−
49	Vc	+	−	±	+	QR	Rs	Qr	QR	−	−
50	Vc	+	−	−	+	Qr	RS	Qr	qRS	+	iso.

liver, the right diaphragm should remain higher than the left in dextroversion. This was not observed in any of our cases.

When the pulmonary vascular markings are within normal limits, the possibilty of complete dextroversion or of mixed dextrocardia is unlikely; whereas if the vascular markings are abnormal, any type of dextrocardia may be present. The demonstration of situs inversus is most helpful since this is present only in Type I or exceptionally in Type III dextrocardia. In order to establish the presence or absence of a partial situs inversus, however, a complete gastrointestinal series must be done. As pointed out earlier, the occurrence of mirror-image dextrocardia without an accompanying situs inversus remains to be proved.

In congenital dextroposition, the heart is at the midline. Except for its unusual location, the cardiac configuration is normal and the apex is directed to the left anteriorly, and downward. The anterior oblique views are normal. This type can be diagnosed with certainty only by means of angiocardiography. The roentgenologic findings noted in Type V dextrocardia with simple dextroposition are similar to those in Type IV dextrocardia, except for the presence of accompanying intra- or extrathoracic anomalies. When the dextroposition is accompanied by midpivotal or severe pivotal rotation, the roentgenologic findings noted in dextroversion are the more salient features. Unlike that noted in Types I, II, and III dextrocardia, the level of the right diaphragm in Types IV and V is still higher than or the same as that of the left diaphragm, even in dextroposition with severe pivotal rotation where the heart is situated entirely on the right side. This implies that the overlying heart exerts maximal influence on the diaphragmatic level during or shortly after full development of the diaphragm, and that the extrinsic cardiac displacement occurs much later in fetal life.

ELECTROCARDIOGRAPHY

The spread of ventricular activation in a normal heart is well known. These electro-

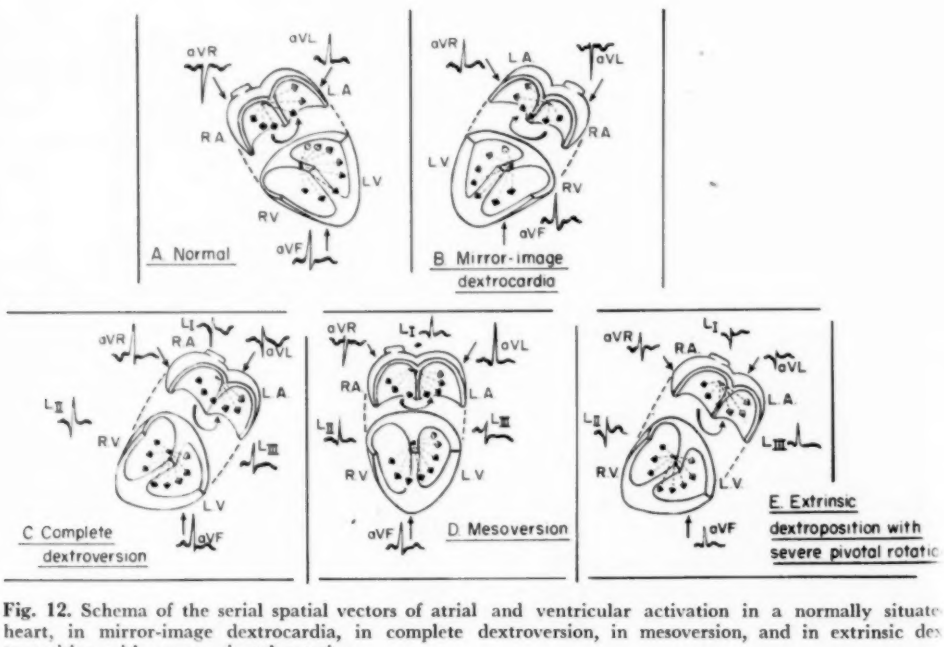

Fig. 12. Schema of the serial spatial vectors of atrial and ventricular activation in a normally situated heart, in mirror-image dextrocardia, in complete dextroversion, in mesoversion, and in extrinsic dextroposition with severe pivotal rotation.

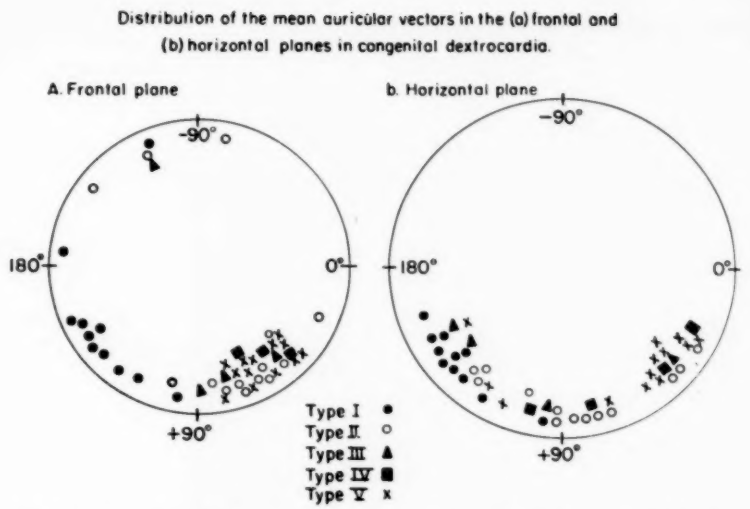

Fig. 13. Distribution of the mean auricular vectors in the frontal and horizontal planes in the various types of congenital dextrocardia.

motive forces generated in a three-dimensional direction should theoretically indicate the true position of the heart. Wolff and co-workers[50] for example have demonstrated the effect of varying degrees of dextroposition and dextrorotation of the heart on the cardiac vectors, particularly on the initial vectors of ventricular activation. Such a correlation, however, between the electrical and anatomic positions of the heart is not always accurate because of the many variables inherent in the electrocardiogram. Indeed studies correlating the anatomic position of the heart determined from biplane angiocardiograms with electrocardiographic findings in children have not been satisfactory.[51]

The typical electrocardiogram in mirror-image dextrocardia is well known.[2, 9, 34, 52, 53] The tracings in Lead aV_R and in Lead aV_L are interchanged. Those in Leads II and III are similarly interchanged while the tracings in Lead I are reversed. In an uncomplicated case the right precordial tracings are similar to those obtained from corresponding normal left precordial leads. In a complicated case, however, these findings are altered by the existing ventricular hypertrophy and the QRS configuration loses its significance. The only nearly constant finding is the inverted P waves in Lead I and usually in the left precordial leads. This almost always, but not invariably, indicates atrial inversion. In dextroversion complex, various tracings have been reported by different authors.[1, 8, 9, 34, 35, 46, 53] Abnormally deep Q waves in Lead I and in Lead II accompanied by negative T waves have been repeatedly described. Other workers[34, 39, 54] have shown abnormal ventricular complexes consisting of an RS pattern over the right precordium and a qRS pattern in the left precordium starting from V_1 or V_2. Similar tracings showing ventricular complexes of the qR type in V_2 or V_3 through V_6 have also been described in dextroposition.[34, 45]

Fig. 12 illustrates the thoretical serial spatial vectors of atrial and ventricular activation in a normal heart, in mirror-image dextrocardia, in complete dextroversion, in mesoversion, and in dextroposition with severe pivotal rotation. The vector forces in Type III dextrocardia partially resemble those in Type I and Type II dextrocardia, depending on which chambers are inverted. In Type IV dextrocardia, they are essentially normal. In Type V dextrocardia, the vectors are also normal in simple dextroposition but

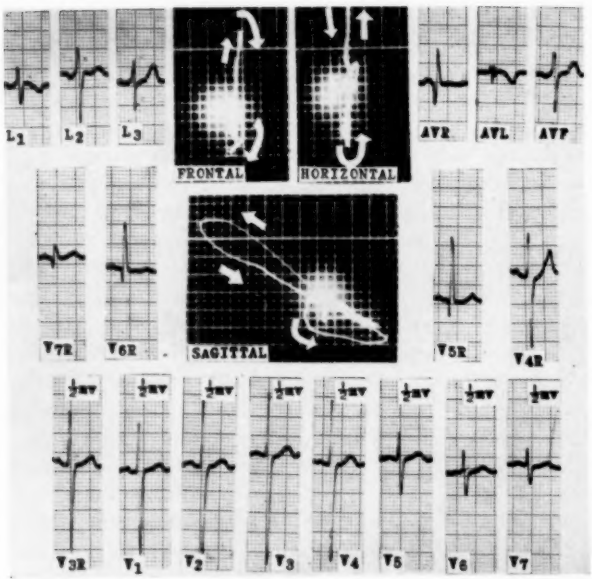

Fig. 14. Electrocardiogram and vectorcardiogram of Case 24 (mesoversion).

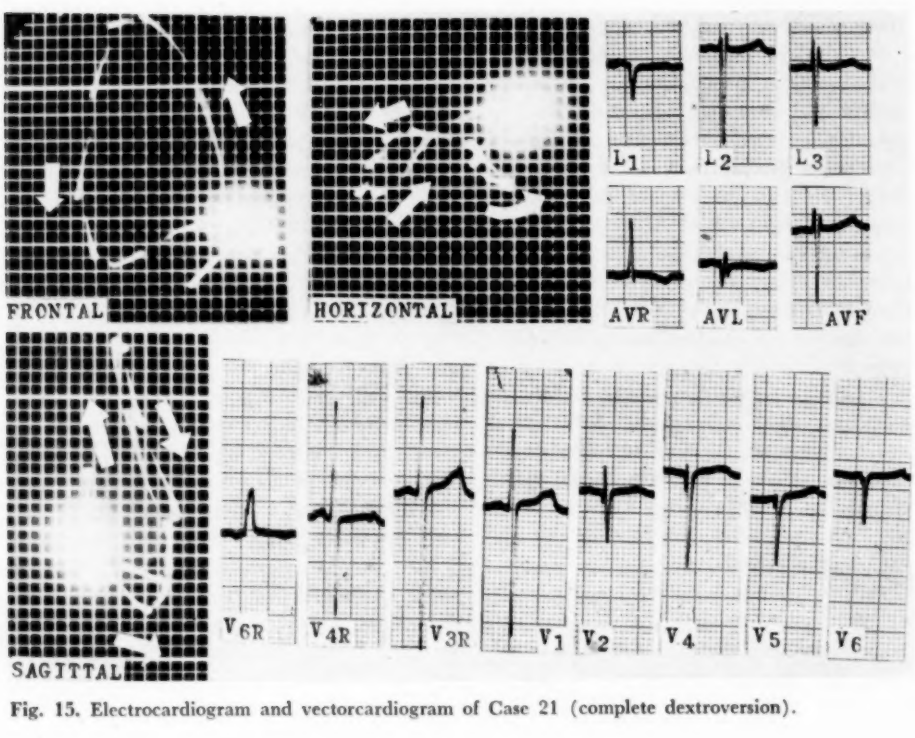

Fig. 15. Electrocardiogram and vectorcardiogram of Case 21 (complete dextroversion).

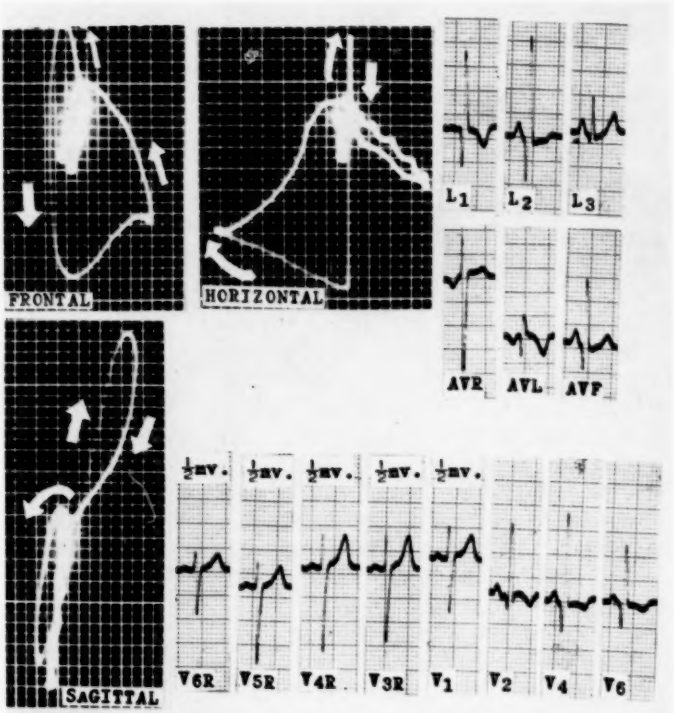

Fig. 16. Electrocardiogram and vectorcardiogram of Case 28 (mixed dextrocardia with ventricular inversion).

when accompanied by pivotal rotation, they resemble those described in complete or incomplete dextroversion. While this schema explains the electrocardiographic patterns wholly on the basis of the abnormal position of the cardiac chambers, it does not consider the effect of chamber hypertrophy which is commonly encountered in Type I, II, and III dextrocardia. Since the right ventricle is the most frequently hypertrophied chamber, it is the magnitude rather than the direction of the mean spatial vectors which is appreciably altered in Types II and III. The electrocardiogram, therefore, remains explicable to a great extent on the basis of the heart's abnormal position. However, when right ventricular hypertrophy occurs in Type I dextrocardia, the direction and magnitude of the vector forces are readily altered because of the proximity of this hypertrophied chamber to the chest wall.

Table IV is a résumé of the electrocardiographic data in our series. The typical previously described tracings in Type I dextrocardia were noted only in the uncomplicated cases (Cases 1 to 5). Inverted P and T waves in Lead I and in Lead aV_L were present in all of our 11 cases. In one of these (Case 11), a nodal rhythm was present with inverted P waves in Lead I, Lead aV_F, and over the left precordial leads. In the complicated cases the diagnosis of right or left ventricular hypertrophy was difficult to ascertain particularly in the precordial tracings since complexes of the qR, Rs, or rsR′ types may be ascribed to hypertrophy of either one or both ventricles. The ventricular complexes in the standard leads appeared most helpful since in 5 cases with right ventricular hypertrophy (Cases 7 to 11), the Lead I tracings showed relatively tall R waves of the QR or qR pattern, unlike another case with tricuspid stenosis

(Case 6) where a Qr complex was noted. These ventricular complexes are in marked contrast to the rSr′ pattern in Lead I in the uncomplicated cases.

The frontal ÂP in the 11 cases with Type I dextrocardia was +145 degrees ±24; in the horizontal plane it was +138 degrees ±31. In contrast, the frontal ÂP of 14 patients with Type II dextrocardia was +53 degrees ±33 and the horizontal ÂP was +87 degrees ±30. The P_I waves were either upright, biphasic, or isoelectric in 11 of the 14 cases with Type II dextrocardia. In 2 patients with a nodal rhythm (Cases 16 and 17) the P waves were upright in one and biphasic in the other. In most instances P_{aVL} was biphasic, isoelectric, or even inverted. This may be explained by the posterior location of the sinus pacemaker in the right atrium in relation to the anteriorly situated left atrium. Since the negative P waves in aVR were greater than the ones registered in aVL, the P waves in Lead I remained upright, biphasic, or at least isoelectric. The distribution of the mean auricular vectors in the frontal and horizontal planes is illustrated in Fig. 13. The distribution of the frontal ÂP in Type I dextrocardia differed from those of the other types. This is due to the abnormal location of the sinus pacemaker on the left side in this type. An inverted P_I, however, does not invariably denote atrial inversion. It may be observed in nodal rhythm with retrograde atrial activation producing either negative or upright P_I waves.[9, 34, 53] It has also been described in proved cases of levocardia without atrial inversion[53] and in a confirmed case of dextroversion with an aneurysmal left atrium,[55] although in this reported case the atrial tachycardia probably accounted for the abnormal P wave. The distribution of ÂP in Type II dextrocardia and in Type V dextrocardia with mid- or severe pivotal rotation was nearly identical in the frontal plane but not in the horizontal plane (Fig.

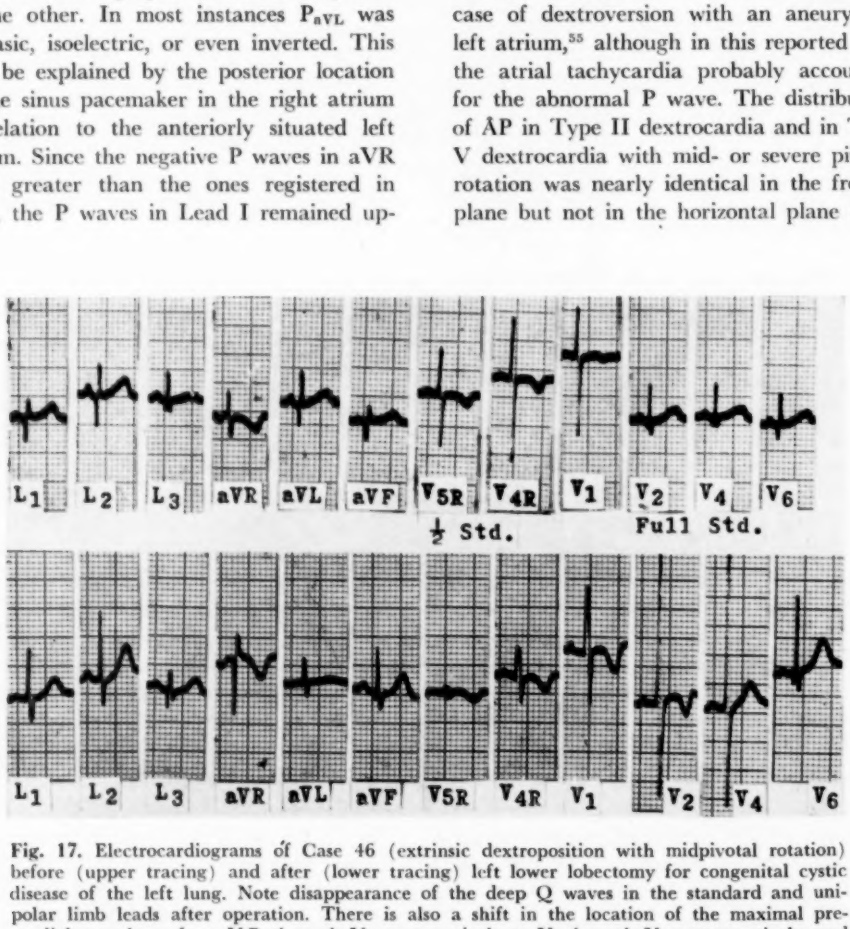

Fig. 17. Electrocardiograms of Case 46 (extrinsic dextroposition with midpivotal rotation) before (upper tracing) and after (lower tracing) left lower lobectomy for congenital cystic disease of the left lung. Note disappearance of the deep Q waves in the standard and unipolar limb leads after operation. There is also a shift in the location of the maximal precordial complexes from V_3R through V_1 preoperatively to V_2 through V_4 postoperatively, and a disappearance of the QR pattern in V_2 through V_6 which was present in the preoperative tracing.

13). The right atrial hypertrophy usually present in the former type and usually absent in the latter probably accounts for this difference. In 2 cases (Cases 13 and 24) of Type II dextrocardia, where the angiocardiograms demonstrated markedly dilated right atria, the P waves in Lead I were slightly negative (Fig. 14). They were upright in Lead aVF in one (Case 13) and biphasic in the other (Case 24). The possibility of a nodal rhythm in the latter case is unlikely since negative P_{AVF} should have been present, considering the fact that the right atrium was markedly dilated. These findings demonstrate that slightly negative P waves in Lead I may rarely be encountered in Type II dextrocardia with markedly dilated right atrium.

Deep Q waves accompanied by negative T waves in Leads I and aVL were noted in 8 of 9 cases with complete dextroversion, whereas this abnormal Q wave was present in only 1 of the 5 cases with mesoversion (Case 26). The schematic diagram in Fig. 12 explains the genesis of these abnormal complexes since the initial QRS vectors are directed to the right superiorly. This is also demonstrated by the frontal vectocardiogram of Case 21. In the presence of right ventricular hypertrophy the QRSsÊ loop is oriented in the right anterior, superior octant (Fig. 15), whereas in tricuspid atresia the initial limb of the QRSsÊ loop is oriented superiorly and posteriorly and to the right where it is followed by a subsequent loop projecting anteriorly, inferiorly, and slightly to the left. The vectocardiogram in mesoversion illustrates the localization of the vector forces in the midchest since the QRSsÊ loop in the frontal and horizontal views are narrow and vertical, whereas in the sagittal plane it is unfolded (Fig. 14). A qR or qRs pattern in V_2 through V_6 was present in 3 of the 5 cases with mesoversion (Cases 22, 25, and 26). This is explained by the location of the left ventricle immediately to the left of the midsternum.[34, 39, 54]

We have found no specific electrocardiographic findings in Type III dextrocardia. The importance of the spatial localization of the P axis and of the distribution in the precordial tracings of the QRS morphologic patterns of the right ventricle (rS or RS) and of the left ventricle (qR or qRs) in the differential diagnosis of dextrocardia has recently been stressed by Portillo and co-authors.[34] Although precordial lead tracings taken predominantly over the right ventricle show ventricular complexes which are usually different from those obtained from the region of the left ventricle, the so-called typical "left ventricular" morphologic patterns may ocasionally be due to a markedly hypertrophied right ventricle. For example, the vectorcardiogram and electrocardiogram of Case 28 were interpreted by us to indicate left ventricular and right atrial hypertrophy (Fig. 16). At necropsy, mixed dextrocardia with ventricular inversion (Type IIIb), right atrioventricular atresia, large atrial septal defect, ventricular septal defect, pulmonary atresia, and double superior venae cavae were found. The huge ventricle situated anteriorly and to the left which undoubtedly accounted for the qR complexes in the precordial tracings was morphologically the right ventricle; the anatomic left ventricle was a diminutive chamber situated to the right, posteriorly and superiorly.

The electrocardiograms in our 3 cases with congenital dextroposition were within normal limits unlike those in previous reports.[45, 46] Since the actual position of the cardiac chambers was not demonstrated by angiocardiography in those reported cases, it is possible that incomplete dextroversion was also present and accounted for the abnormal precordial tracings. In Type V dextrocardia with simple dextroposition, the tracings are similarly normal. In 9 of our 10 cases where the dextroposition was accompanied by midpivotal or severe pivotal rotation, deep Q waves in Leads I and aVL similar to those described in complete dextroversion were noted. The accompanying T waves were, however, upright in the majority of these. In 6 cases where the extrinsic causes for the cardiac displacement

were corrected surgically, the electrocardiogram reverted to normal (Fig. 17).

SUMMARY

Fifty cases of congenital dextrocardia were studied and classified into 5 major types. In Type I dextrocardia (mirror-image dextrocardia) the anatomic right atrium and right ventricle are situated to the left of and anterior to the corresponding systemic chambers. A mirror-image arrangement of the cardiac chambers is present since the frontal relationship of the chambers is reversed, yet, the anteroposterior arrangement is normal. In Type II dextrocardia (dextroversion complex) the relations of the cardiac chambers are normal; the right atrium and right ventricle are situated to the right of and posterior to the corresponding systemic chambers. In complete dextroversion the cardiac apex is situated anteriorly and to the right; in incomplete dextroversion or mesoversion, it is located in the substernal region and the longitudinal axis of the heart is parallel to the midsagittal axis of the chest. Type III dextrocardia (mixed dextrocardia) is characterized by inversion of the atria alone or of the ventricles alone. The arrangement of the cardiac chambers is therefore in part similar to that of Type I and of Type II dextrocardia. In Type IV dextrocardia (congenital dextroposition) the heart is in the midchest, but the arrangement of the chambers is normal and the cardiac apex is still directed to the left and anteriorly. Types I, II, III, and IV represent the intrinsic group of dextrocardia, since the cardiac heterotaxy is caused by a developmental anomaly of the primitive heart tube. In Type V dextrocardia (congenital extrinsic) the abnormal position of the heart is due to its displacement by congenital anomalies of the lungs, diaphragm, or chest cage. The rightward displacement may be in the frontal plane only (simple dextroposition) or may occur in both the frontal and horizontal planes (dextroposition with pivotal rotation). The various types of dextrocardia are illustrated by angiocardiograms.

The incidence of cardiac anomalies in the intrinsic group was 79 per cent, and in the extrinsic group 24 per cent. These anomalies were, as a rule, multiple and severe and together formed specific anatomic syndromes usually characterized clinically by dextrocardia, cyanosis, and diminished pulmonary blood flow. The most common entities encountered were tetralogy, single ventricle with pulmonary stenosis, and tricuspid atresia or stenosis.

The chest roentgenologic findings in Types I, II, and III are similar in most respects, consisting of an elevated left diaphragm and identical cardiac configurations in the posteroanterior and in the oblique views which are the reverse of the normal. A right aortic arch is common in Type I dextrocardia. Situs inversus always accompanies this type. The previously reported cases of isolated mirror-image dextrocardia are probably Type II or possibly Type III dextrocardia. In Type IV dextrocardia the heart shadow is medially located in the frontal view and assumes normal configuration in the oblique chest roentgenograms.

Negative P waves in Lead I generally indicate atrial inversion, as occurs in Type I and occasionally in Type III dextrocardia, but they may be observed in other conditions not associated with atrial inversion as in nodal rhythm, in levocardia, and in atrial tachycardia. On 2 occasions we have observed slightly negative P_I waves in dextroversion with marked right atrial enlargement. The rSr′ ventricular pattern in Lead I as well as the interchanged tracings of Leads aVR and II with those of Leads aVL and III, respectively, is typical of uncomplicated Type I dextrocardia. In the presence of right ventricular hypertrophy a constantly observed change is a relatively tall R wave in Lead I of the QR or qR pattern. The tracings in complete dextroversion characteristically consist of flattened but upright P waves in Lead I and deep Q waves in Leads I, II, and aVL with negative T waves. Similar tracings are seen in Type V dextrocardia when the dextro-

position is accompanied by severe pivotal rotation. The T waves in these cases are, however, more often upright than negative. Only 1 of the 5 cases with incomplete dextroversion had similar abnormal Q waves in Leads I and aVL; a qRs pattern in V_2 through V_6 was present in 3. There are no typical electrocardiographic findings in Type III dextrocardia. The tracings in Type IV dextrocardia are normal.

Most of the electrocardiographic changes described may be explained by the abnormal position and location of the cardiac chambers. These are demonstrated by means of schematic vector analysis and illustrated by actual vectorcardiograms.

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Favism in a nursing infant

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THE clinical manifestations of favism are those of an acute, severe hemolytic anemia. In a susceptible individual the syndrome of favism can be caused by eating the *Vicia fava* beans, inhaling its pollen, or drinking milk from a mother who has ingested the beans.[1]

Many detailed descriptions of this disease have appeared in the literature of several Mediterranean countries.[2, 3, 4] The first report of favism in the U. S. appeared in 1933[5] and since then numerous other cases have been documented.[6-19] Favism in the United States is probably far more common than the number of reported cases would indicate. A high index of suspicion, familiarity with the syndrome, and the recent availability of red cell enzyme studies should allow for far more frequent diagnosis. In recent years the pathogenesis of favism has been defined. The susceptible patients and members of their families have an inborn enzymatic defect of the erythrocytes, characterized by a deficiency of glucose-6-phosphate dehydrogenase, a decreased level of glutathione and reduced glutathione stability.[20]

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The present case was that of a 4-month-old female nursing infant. It is the second case of its kind to be reported and the first in which the patient survived.[1]

CASE REPORT

A. A., a 4-month-old female infant, the second child of healthy Jewish parents, immigrants from Egypt, was born after a normal pregnancy and delivery. Birth weight was 3,000 grams. Feedings consisted of breast milk and cereals. A month prior to admission the child had bronchitis and was treated with antibiotics; recovery was complete. Three days prior to admission, the child's mother ate fava beans. A day later the parents noticed that the baby's skin turned yellow. She was taken to a physician who referred her to the hospital. Fava beans were a regular part of the family diet; there was no history of favism in the family, however.

On admission the patient was acutely ill and apathetic; the skin and mucous membranes were pale and yellow. The heart rate was 180 per minute, and respirations, 60 per minute. The temperature was 36.8° C. Physical examination revealed the spleen to be 1 cm. and the liver 2 cm. below the costal margins, respectively. The lungs were clear. The urine was dark with increased urobilinogen content, 1:220. The red blood cell count was 1 million per cubic millimeter.

Table I. Blood glutathione level in milligrams per 100 c.c. erythrocytes

Day after onset	*Age*	*Before incubation*	*After incubation with APH*
Patient 3rd day	4 mo.	55 mg./100 c.c. RBC	41 mg./100 c.c. RBC
Patient 9th day	4 mo.	69 mg./100 c.c. RBC	24 mg./100 c.c. RBC
Patient 44th day	5 mo.	58 mg./100 c.c. RBC	4 mg./100 c.c. RBC
Mother	24 yr.	70 mg./100 c.c. RBC	11 mg./100 c.c. RBC
Father	34 yr.	46 mg./100 c.c. RBC	32 mg./100 c.c. RBC

Because of her critical condition, the patient was placed in oxygen and given 150 c.c. of whole blood, Achromycin 50 mg. per kilogram, and prednisone 10 mg. every 12 hours.

The following morning her condition had improved. The skin was somewhat more icteric, the temperature had risen to 38.8° C. Excessive urobilinogen was still demonstrated. The hemoglobin rose to 5.7 Gm. and the erythrocyte count to 1.8 million per cubic millimeter. The leukocyte count was 25,000 with a marked shift to the left and a reticulocytosis of 8.8 per cent. The indirect bilirubin was 3.4 mg. per cent; the direct bilirubin was 0.9 mg. per cent. The direct and indirect Coombs tests were negative. A second blood transfusion of 100 c.c. was given, and her condition steadily improved. The urobilinogen in the urine became normal. On the third day the hemoglobin was 8.7 Gm. per cent and the erythrocyte count 2.3 million per cubic millimeter, with a reticulocytosis of 12 per cent.

RED BLOOD CELL STUDIES

The reduced glutathione (GSH) in the red cells, 2 days following the initial blood transfusion[21, 22] was 55 mg. per 100 c.c. of erythrocytes before incubation with acetylphenylhydrazine (APH), and 41 mg. per 100 c.c. erythrocytes after incubation. The normal range by this method is 70 mg. per 100 c.c. of red cells. Persons sensitive to fava beans or to certain drugs generally have values below 60 mg. per 100 c.c. of red cells. The GSH stability test was performed by the method of Beutler.[23] Decrease of the GSH level below 30 mg. per 100 c.c. of red cells after incubation of the blood with acetylphenylhydrazine is considered a characteristic of the erythrocyte abnormality in favism. Glutathione values between 30 mg. and 40 mg. per 100 c.c. of erythrocytes are found regularly among females in the affected families, but since similar values may be occasionally found in normal males and females, these values are not considered proof of the presence of the enzymatic abnormality.

In the case described repeated studies* of the erythrocyte glutathione level and stability demonstrated the presence of the classic enzymatic abnormality described in favism. Similar studies performed on the parents revealed the mother to be a carrier of the enzymatic deficiency, and the father a probable carrier (Table I).

DISCUSSION

In the past few years, increased attention has been given to the enzymatic defect in favism,[24-26] congenital nonspherocytic hemolytic anemia,[27] and hemolysis due to drugs such as primaquine,[28-29] sulfonamides,[24, 26] and naphthalene.[30-31] The defect in the erythrocyte is characterized by a deficiency of glucose-6-phosphate dehydrogenase, low glutathione content, and glutathione instability after treatment with acetyl-phenylhydrazine.[20] Transient instability of reduced glutathione was demonstrated by Zinkham and Childs[31] in the red blood cells of normal white newborn infants, but these values revert to normal after a few days of life. These infants demonstrate a strikingly high level of glucose-6-phosphate dehydrogenase through the first year of life.

The normal glutathione level with and without acetyl-phenylhydrazine found in the

*The tests were performed in the Biochemical Laboratories of Tel Hashomer Government Hospital, Tel Hashomer, Israel.

original examination was due to transfused normal red blood cells and the reticulocytosis.[35]

Six weeks after the initial episode the tests were diagnostic of the enzymatic deficiency.

The patient reported upon here and his parents are Oriental Jewish immigrants from Egypt. Szeinberg and Sheba[32] showed that the enzymatic defect is common in families of Shephardic origin and Oriental Jews (immigrants from Mediterranean, Middle East, and North African countries). The defect occurs only rarely among Ashkenazic Jews (Anglo-Saxons or Jewish immigrants from non-Mediterranean Europe).

Marked glutathione instability of the mother's red blood cells occurred only after incubation with acetyl-phenylhydrazine. The mother gave no history of favism or hemolysis due to drugs. The glutathione level before and after incubation with APH in the father's erythrocytes was equivocal. The GSH level in the father's blood of 46 mg. per 100 c.c. red cells was definitely below normal limits, but, after incubation with APH, the GSH fell to only 32 mg. per 100 c.c. red blood cells. Similar findings have been demonstrated in females with an intermediate form of the disorder. To my knowledge this has not been previously described in males.

The hereditary basis for the disease has been shown to be a sex-linked, incompletely dominant gene with variable expressivity.[33, 34] Both parents of the affected female infant demonstrated glutathione instability, the father to a lesser degree than the mother. It appears, therefore, that the affected female child probably was homozygous for the gene for glucose-6-phosphate deficiency.

The case described here is of interest because the transmission of the active factor of the fava bean was through the mother's milk, and because the patient was a female. There is still no explanation as to the cause of the activation of the reaction which produces the hemolysis. This must be known before the etiology of favism is completely understood.

SUMMARY

1. A case of favism in a breast-fed infant of Mediterranean parents has been described.

2. Glutathione levels and glutathione instability were measured and found to be abnormal during the recovery period.

3. The reactive substance in fava beans which induces hemolytic anemia in glucose-6-phosphate deficient individuals was transmitted through the mother's milk.

4. The affected female infant most likely represents the homozygous state for a sex-linked disorder.

5. Jaundiced breast-fed children from parents of Mediterranean countries should be watched for favism.

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Meconium peritonitis presenting as an abdominal mass

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A RARE complication of an uncommon disease, meconium peritonitis, presenting as a relatively common problem, an abdominal mass in the newborn infant, is of sufficient interest to be reported.

Longino and Martin[1] state that of 32 abdominal masses in neonates, 17 originated from the urinary tract and 5 from the female genital tract. Single examples of hepatic cyst, duplication and volvulus of the ileum, choledochal cyst, distended gall bladder and mesenteric cyst, as well as single examples of 4 solid tumors, teratoma, neuroblastoma, leiomyosarcoma, and hepatoma complete their list. Potter,[2] Gross and Ladd,[3] and Andersen[4] add the possibilities of dilated intestine proximal to stenosis or atresia, cyst of the urachus, distended urinary bladder, Meckel's diverticulum, dermoid cyst, ganglioneuroma, and chromaffinoma. Pseudocysts of the pancreas have been described in children.[5]

Just as discussions of tumors in the abdomen of newborn infants do not mention meconium peritonitis, most descriptions of meconium peritonitis do not mention the possibility that the presenting symptom may be a mass.[6, 8, 9, 15-23] Four instances of meconium peritonitis have been described in association with an abdominal mass. Dubler[10] in 1888 reviewed in detail the pathologic findings in an infant who had an oval cystic lesion measuring 3.5 cm. in length that he felt was formed by slow leakage of meconium from a defect in the wall of the large intestine. Low, Cooper, and Cosby[11] and Brunkow and co-workers[7] depicted indefinite right lower quadrant masses formed by adhesions binding the intestine tightly about a meconium abscess. The second of 2 cases reviewed by Packard and Reynolds[12] is almost identical to the protocol reported in this paper.

CASE REPORT

K. J. P., a full-term white female infant weighing 2,870 grams, was born with a macerated twin at United States Army Hospital, Fort Hood, Texas, on Jan. 3, 1959. The infant's large protuberant abdomen made delivery difficult. The pale, gray infant breathed spontaneously but weakly. The skin of the abdomen was a mottled, nonblanching purplish color suggestive of ecchymosis. The abdomen, tense but neither tender nor rigid, was distended by a fixed, perfectly globular mass 12 cm. in diameter that felt cystic, could not be separated from the liver, and was dull to percussion. Peri-

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stalsis was heard, and tympany was percussed in the left upper quadrant shortly after birth. The rectum was tight and light yellow-green mucus appeared on the gloved finger. Gastric suction withdrew 2 c.c. of thick blood mixed with dark green mucus. Catheterization of the urinary bladder produced 10 c.c. of normal urine. None of these procedures changed the size or tension of the cystic mass. An abdominal radiograph taken shortly after birth showed small gas-filled loops of bowel crowded into the left upper quadrant and a homogenous radiopaque mass in the midabdomen.

Twelve hours later an intravenous pyelogram showed normal kidneys, the mass distended with gas but no air visible in the rectum (Fig. 1). Physical examination showed little change except for the appearance of a loud tympanitic percussion note over the abdominal mass. No meconium had passed through the anus.

An exploratory laparotomy was performed because of the high probability of an intestinal obstruction. The possibilities of a duplication of the intestine communicating with the lumen, a cystic dilatation of the intestine incarcerated in a volvulus, or a cystic dilation of the intestine proximal to a volvulus, atresia, or stenosis were considered. When the thickened, opaque, parietal peritoneum was opened, the incision extended directly into a thick-walled abscess containing meconium and gas. Dissection into the left upper quadrant revealed a small free peritoneal space where a segment of the small intestine was twisted 360 degrees upon itself. The remainder of the bowel was adherent to itself and tightly bound into the wall of a pseudocyst that extended from the inferior surface of the liver to the urinary bladder and down into the pelvis. Twenty centimeters proximal to the ileocecal valve a perforation was found. Proximal to the perforation the gut was distended, but distally it was narrowed despite its meconium contents. The perforation was resected, and an end-to-end anastomosis performed. Attempts to remove the pseudocyst and to free adherent, kinked bowel produced such profuse oozing of blood as to necessitate closure of the abdomen after removal of free meconium and only a portion of the "cyst" wall. The infant died the day following the operation without having passed meconium per rectum.

Necropsy findings. At postmortem examination the abdomen was noted to contain 25 c.c. of serofibrinous fluid and remnants of what once was a thick, fibrous wall forming a cystic cavity and adhering to the peritoneal surfaces of the liver, anterior abdominal wall, spleen, intestines, and uterus. Many areas of the intestine were discolored purple, suggestive of hemorrhage. Attempts to strip away the conglomerating pseudocyst wall produced a simultaneous removal of visceral peritoneum as well as

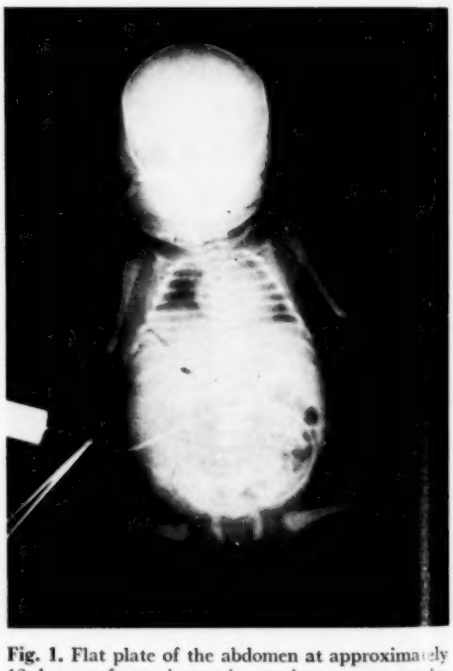

Fig. 1. Flat plate of the abdomen at approximately 12 hours of age just prior to intravenous pyelogram (dye-filled syringe and umbilical intravenous catheter) shows dilated loops of bowel crowded into the left upper quadrant and left flank by a large globular air and fluid-containing mass in the midabdomen. Minute calcifications in the pseudocyst wall are not visible in the reproduced radiograph.

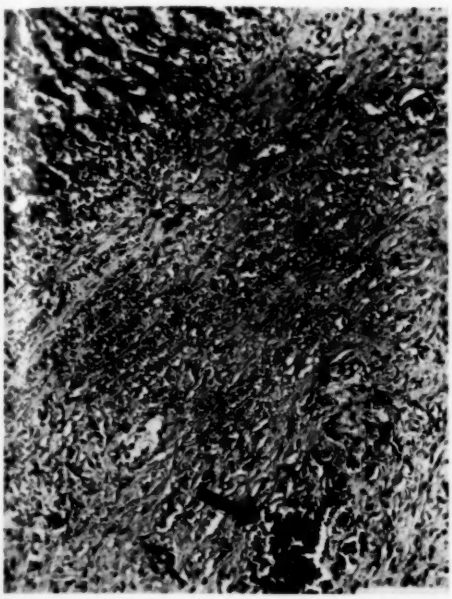

Fig. 2. Photomicrograph of the pseudocyst wall stained by the hematoxylin-eosin method shows marked fibrosis with minimal chronic inflammatory changes and numerous calcium plaques (arrow), lesser amounts of keratin, and hemosiderin as well as a few macrophages, polymorphonuclear leukocytes, lymphocytic and large round cells. The pseudocyst wall obliterates the liver capsule and appears immediately adjacent to the liver (left upper quadrant).

muscle tissue. Meconium of usual consistency and gas had passed the anastomosis.

Microscopically, the pseudocyst wall was composed of dense, fibrous tissue blending indistinguishably with the visceral peritoneum (Fig. 2). The liver and pancreas were normal.

Pathologic diagnoses were: (1) volvulus, corrected by operation; (2) perforation of the ileum, resected by operation; (3) functional ileoileostomy, not healed; (4) meconium peritonitis, old and well organized; (5) inflammatory pseudocyst of the peritoneum; and (6) atelectasis of the lungs, mild.

DISCUSSION

Meconium peritonitis usually presents as a distended, tympanitic doughy abdomen in a pale, cyanotic, and listless infant with edema of the abdominal wall, external genitals, and lower extremities.[6-9] Vomiting of bilious material is commonly present and meconium stools may or may not be. The classic radiographic triad of opaque calcifications, free air under the diaphragm, and air and fluid levels in dilated loops of bowel has been described by Neuhauser.[13]

Pathologic findings consistent with the diagnosis of meconium peritonitis have been described by many.[2, 12, 14-19] Most authors mention the 5 basic findings of fibrosis, chronic inflammation, meconium in the peritoneal space, calcareous deposits, and absence of infection. The degree of fibrosis (usually in inverse proportion to the degree of inflammation) correlates with the duration of the process.

The data in our case report meet the clinical and pathologic criteria sufficiently to warrant an unequivocal diagnosis of localized meconium peritonitis. The classical findings described with generalized, acute meconium peritonitis were somewhat obscured by the formation of a pseudocyst. Packard and Reynolds[12] and Forshall and co-workers[14] mention abscess formation as an aspect of sterile meconium peritonitis. Localization of peritonitis following rupture of a hollow viscus is less frequent in childhood than in adulthood because of the small omentum and relatively poor resistance to infection present during early life.[3, 20] The tendency of meconium peritonitis to localize and form a pseudocyst can be attributed to a slow or intermittent escape of meconium as well as to a marked inflammatory response initiated by the extremely tenacious and irritative properties of meconium.

Abdominal distention, a readily palpable abdominal mass, changes in the abdominal wall and intra-abdominal radiopacities were prominent signs in 4 of the 5 cases of meconium peritonitis associated with a mass. The oddly discolored abdominal skin described in the protocol was more consistent with a process of greater duration than could be accounted for by trauma at the time of delivery and was more consistent with the changes mentioned by Gilbert and

Ramey[21] as characteristic of meconium peritonitis. Despite preoperative examination for radiopacities, fine curvilinear shadows apparently in the pseudocyst wall were not noted until the roentgenograms were carefully studied post mortem. White[22] states that approximately 75 per cent of cases of meconium peritonitis have calcifications that are demonstrable by radiography.

No other report of any other abdominal mass of the newborn infant could be found that has the following diagnostic criteria: (1) peculiar skin changes described as characteristic of meconium peritonitis, (2) radiographic evidence of a cystic lesion communicating with the intestinal lumen, and (3) radiographic evidence of calcification of the cystic mass. It is felt that the combination of these findings is diagnostic of meconium pseudocyst formation communicating with the intestine.

Interest in diagnosis and management has been stimulated by the recent increase in survival of infants born with meconium peritonitis.[23] Authors writing in the last few years agree that surgical exploration is urgently indicated to relieve an obstruction and close a perforation if either is present.[6, 21-23] Cleansing the peritoneum of adhesions and meconium is a third indication for operation. It is relatively easy and is associated with a much better prognosis when the perforation is acute.[9, 12, 22, 23] Dense, heavily calcified adhesions found when perforation has occurred relatively early in gestation cannot be removed without injury to underlying organs but, if the adhesions do not prevent effective peristalsis, they may be absorbed.[7, 11]

SUMMARY

The clinical and radiographic diagnostic features of meconium peritonitis with pseudocyst formation that separate this entity from other types of abdominal tumors have been described, and an additional case has been presented.

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An evaluation of resident training in the outpatient department

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THE overwhelming progress in the field of medical science which continues to accumulate facts at a rate far faster than the human mind is able to absorb them has produced equally great changes in the practice of medicine. The elimination of many of the serious infectious diseases through the development of effective public health measures and the use of Ehrlich's "magic bullets" has so reduced the mortality rate that the physician has been forced to be more concerned with the promotion of health and less concerned with the saving of life than was his predecessor of 30 to 40 years ago.

The patient of today asks that his physician do more than keep him alive or treat him when he is ill or hurt. At an ever-increasing rate, he expects his physician to keep him healthy and happy.[1]

Some remarkable experiments in undergraduate education have evolved from the recent efforts to re-evaluate the medical school curriculum.[2-6] The program at Western Reserve University has achieved the most dramatic changes, but many other schools have experimented with a new approach. In contrast to this, there has been very little change in pediatric training as conducted at the resident physician level.

The discontent with some of the existing programs of training and with the practice of pediatrics has been evident for several years. Such discontent is not universal, but it is common enough to be a cause for real concern. Recently, as evidenced by discussions of the "new pediatrics,"[7] there has been increased editorial attention focused on this problem.

Like the weather and taxes, this problem has been talked about, but thus far the talk has resulted in a minimum of change. The differences which do exist between various training centers are probably due more to circumstance (i.e., the size of the city, the research orientation of the staff, and the service load of the hospital) than to planning.

In early 1959 a questionnaire was prepared and mailed to 25 pediatric teaching centers throughout the country. From this mailing there were 18 completed replies. Each of the 18 centers was associated with a medical school. Three were located in New York, 3 in Ohio, 2 in Massachusetts, 2 in Michigan, 2 in California and one each in North Carolina, Connecticut, Georgia, Florida, Pennsylvania, and Illinois. Based

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on figures from the 1959 Residency Number of the *Journal of the American Medical Association,* 333 pediatric residents (18 per cent of the total) received their training in these institutions. This report is based on information from these replies. Excellent cooperation was obtained from the various departments and I am indebted to those who took the time to answer. Many replies were accompanied by letters or long discussions of the problem.

The questionnaire was concerned with the problem of training pediatric residents and straight interns in the outpatient department because this portion of the training is most in need of attention. All training offered in the emergency room, well-baby clinic, pediatric clinics, and specialty clinics was considered as part of the outpatient department program.

Table I. Percentage of time spent in outpatient department (including general pediatric clinics, well-baby clinics, specialty clinics, and emergency room

	First year (%)	*Second year (%)*	*Average of 2 years (%)*
Maximum	50	75	54.0
Minimum	10	25	17.5
Average	30	39	35.0

Table II. Work load per day in number of patients seen by each resident

Clinic	*Maximum*	*Minimum*	*Average*
1	10	2	6
2	10	3	7
3	25	5	6
4	20	5	10
5	20	5	10
6	15	7	10
7	12	4	9
8	25	15	20
9	24	6	16
10	30	10	20
11	?	?	12
12	15	9	5
13	12	5	8
14	10	3	6
15	15	7	10
16	20	10	15
17	12	2	7
18	10	4	6
Average	16	5.7	10.5

Table III. Answers to question on amount of time spent on one patient

Answer	*No. of clinics*
Yes	11
Yes (new patients get 1½ hours)	2
Yes (on most days)	1
Usually not	2
Yes (but usually only 30 minutes is spent on a new patient)	1
No answer	1

RESULTS

Among the questions asked were: what percentage of time did each resident spend in the outpatient department; what was the work load in the pediatric clinic and the emergency room; were the residents given an opportunity to have their own follow-up clinic; did the resident have experience with well babies; how was supervision accomplished; was psychiatric consultation available in the clinic; were outpatient department conferences held; and was the training program evaluated by the use of a formal program of contacting former residents?

Time in the outpatient department. The amount of time spent in the outpatient department varied widely from a maximum of 54 per cent to a minimum of 17.5 per cent. The pertinent data are listed in Table I.

Work load. The work load in the general pediatric clinic also varied considerably. The work load was evaluated in terms of the number of patients seen per working day, a working day being defined as a morning and an afternoon clinic session. For most clinics each half day represents a 2 to 3 hour working period, so that a work day would consist of 5 to 6 hours' working time. If the residents actually worked for only a half day at a time, these figures were doubled to make them comparable with the others.

Figures such as those in Table II do not prove much because so many variables are involved. Such things as the type of patient seen, the experience of the resident

Table IV. Residents' follow-up clinic

	No. of clinics
Have follow-up clinic with assigned time	13
Have follow-up clinic without assigned time	2
Have no follow-up clinic	3

Table V. Experience in well-baby care

	No. of institutions
Continuous care well-baby experience	10
Fragmented care well-baby experience	4
No well-baby experience	4

staff working in the clinic, and so forth, will affect the ideal work load. The comments received in answer to this question, discussions with medical directors of several outpatient departments, and personal experience all indicate that an excessive work load continues to be a major factor in preventing the establishment of an effective training program.

Answers to the question, "Can your residents spend as much time as one hour working up any one patient?" are shown in Table III.

The work load in the emergency room varied tremendously. One center had no emergency room service and one had only a night service. In the other 16 centers, the average number of patients seen by one resident during a 7 hour period ranged from a low of 3 to a high of 50. The average of all 16 centers was 18 patients in a 7 hour period. In 7 of the hospitals each resident saw 20 or more patients during each 7 hour period. These figures represent averages,

Table VI. Availability of psychiatric consultation in outpatient department

Type of service	*No. of clinics*
Psychiatrist easily available	6
Psychiatrist available at a scheduled time and for emergencies	6
Psychiatrist on call, but sometimes hard to get	2
Inconclusive answer	1
No psychiatrist available	3

so the maximum number of patients seen is considerably higher.

Follow-up clinics. Fifteen of these 18 training centers provide their residents with a specific period each week in which to see their own patients. In most centers, the follow-up clinic continued during the entire two years of the residency. Three centers had none. The time allotted to the follow-up clinic varied considerably: 11 centers set aside 2 to 6 hours per week for this purpose. This was usually one afternoon per week; one center had 2 afternoons per week, 2 had one hour per week, and 2 had no specifically assigned period for this purpose. Table IV lists the data.

Well-baby experience. The amount of experience pediatric residents get in the care of well babies is shown in Table V.

The resident's well-baby experience is obtained in 10 centers by following the same well babies (or whole families) in his own clinic during his entire residency. Several institutions have combined this with the residents' follow-up clinic. In three training centers, the well-baby experience is obtained by spending a certain number of hours per week during a block of time in a well-baby clinic. City well-baby clinics are frequently used for this purpose. One center has 4 hours per week for 14 weeks; another, 2 hours a week for 8 weeks; and the third, 2 times a week for 6 months. In one clinic, the well-baby clinic ran continuously, but the residents did not follow their own patients.

Supervision. Supervision in the pediatric clinic was accomplished in much the same way in all clinics. The supervision in all 18 centers was done by the full-time and part-time attending staff. A chief resident was also used in 11 of the 18 clinics. In most places the intern or resident worked alone, but had easy access to a consultant who was usually in the clinic during working hours. In general, the supervison seemed good to excellent. Only 2 of the 18 clinics indicated that the supervision was inadequate. In 12 clinics, review of the records was also used as an aid in the program of supervision.

Table VII. Outpatient department conferences

Conferences	No. of clinics
Regular conferences 4 to 5 hours per week	4
Regular conferences 2 to 3 hours per week	2
Regular conferences 1 hour per week	4
Regular conferences less than an hour per week	1
General pediatric clinic conferences	11
Conferences held in specialty clinics only	2
No conferences held	5

A psychiatric consultant was available in 15 clinics but not in the 3 others. In the clinics with psychiatric consultation, there was considerable variability in how this functioned. Table VI gives the pertinent data.

Outpatient department conferences. The use of conferences as a means of education in the outpatient department is just as logical as its use with inpatients. Ten of the 18 clinics had well-organized conferences in the general pediatric clinics, as summarized in Table VII.

Evaluation of training by former residents. Of the 18 training centers, only 2 reported that they had a formal program for evaluating their training through the help of former residents. Fourteen answered "No" to this question. Two failed to answer.

DISCUSSION

The purpose of this survey was to focus attention on the problem of adequate training for pediatric residents, especially as related to the clinic and office practice of this specialty. Most training programs do an excellent job of training the resident to take care of the child who is ill with a serious disease or who presents a diagnostic problem. These are the children who are hospitalized and usually serve as the basis for conferences and teaching sessions. While this part of the training program could undoubtedly be improved, it is already very good.

The resident emerges well equipped to take care of the hospitalized child (of which there are few), but poorly equipped to handle many of the problems which he faces in his office practice. Some of these are fairly minor and he can learn to deal with them quickly on his own. Others are complex and difficult problems for which he needs training.

The results of this survey indicate several areas which need attention. The major problems raised by this questionnaire are: size of patient load, percentage of time spent in outpatient department, well-baby experience, and program evaluation.

The size of the patient load can be a significant factor in resident training. As shown by this survey, some institutions have a relatively small patient load; others have large indigent or semi-indigent clinics, and frequently the service load is so large that there is little time left for training. This should be changed, and it seems reasonable to ask the accreditation boards to establish minimum standards for the outpatient department training of pediatric residents. One of the main factors which must be considered in evaluating the adequacy of a training program is the patient load. Other factors are also important, but when the pressure of service needs becomes too great, all is lost.

In this survey, the percentage of time spent in the outpatient department varied from a high of 54 to a low of 17.5 per cent. It is doubtful that either of the figures represents an ideal percentage of time. It is obvious that merely spending time in the outpatient department is not enough. If the program is devoted to service only, without training value, it is worse than nothing, since it then takes time which could be more profitably spent in other ways. With careful evaluation, it should be possible to define a reasonable ideal division of time.

One of the chief jobs of any practicing pediatrician is the care of well children. In view of this, it is rather amazing that only 10 of the 18 clinics provided continuous care well-baby clinic experience, and that 4 provided no nexperience whatsoever in the care of well children. The mere presence of a well-baby clinic does not assure ade-

quate training but it is obvious that training cannot be adequate without such experience.

Perhaps one reason why pediatric training has not kept pace with the needs of practice is revealed by the fact that only 2 of the 18 centers have a formal method of evaluating their program through contacts with former residents. Such an evaluation program might be a real eye opener to many institutions.

The following recommendations are made as a means of obtaining an improvement in resident training programs:

1. Accreditation boards should be encouraged to evaluate all phases of pediatric training and should pay special heed to the outpatient department training, since so little emphasis has been placed on this in the past.

2. Some effort should be made to obtain minimum standards for pediatric training under the auspices of the Boards, the Academy, or some other national organization.

3. Each training center should make a critical and periodic evaluation of its own training program. This should be a continuing process and should certainly include a survey of graduates of that program.

SUMMARY

A questionnaire was sent to 25 pediatric training centers. Adequate replies were received from 18.

This report deals with the following items:

1. The percentage of the residents' time spent in the outpatient department.

2. The work load in the clinic.

3. The supervision in the clinic.

4. The opportunity for residents to see well babies and follow their own patients.

5. The use of outpatient department conferences.

6. Evaluation of the training program by former residents.

The need for a thorough re-evaluation of the resident training program is emphasized.

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TROPICAL PEDIATRICS

Pediatrics in an industrialized part of Africa

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EXPANSION of secondary industries during and after World War II attracted several hundred thousand Africans† from rural districts to Johannesburg. Of the one million inhabitants of Johannesburg, 650,000 are Africans. Most of the breadwinners are semiliterate. The men are largely employed as unskilled or semiskilled laborers in secondary industries (mine laborers are not included in the above figures), while many women work as factory hands and as domestic servants. There are relatively few African civil servants, professional men, and small traders. In contrast to almost any other part of this continent, this area has practically no agricultural workers.

Nearly all these people live in mass-produced houses in townships covering 30 square miles in the vicinity of this hospital (Fig. 1). It ought to be easy to present a comprehensive picture of the pediatric problems of this district, because registration of births and deaths is compulsory, streets are named, houses are numbered, and free medical services for minor illnesses are provided by 9 polyclinics.* However, the following example shows that information, even from this relatively well-developed part of Africa, may still lack accuracy.

From the data in Fig. 2 it appears that there has been a most gratifying decrease in the African infant mortality rate, i.e., the number of infant deaths per 1,000 live births. This rate, however, can be meaningful only if it is based on the true number of births and deaths. In Johannesburg, African deaths have been notified satisfactorily for several decades, because permission for a burial is granted only after the issue of a death certificate. In contrast, registration of births has always been incomplete, although the proportion remaining unregistered has fallen over the years. This is confirmed by an apparent rise in the birth rate from 20 in 1950 to 32.55 in 1958 (the white birth rate has remained practically unchanged during this period). The above-mentioned decline in the infant mortality rate is, therefore, largely

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†*In many parts of Africa the indigenous population is referred to as "African" and the white population as "European."*

*Since the beginning of 1960 fees are being charged.

illusory and indicates the increasing desire of urbanized Africans to register the births of their children.[1]

The official figures for the infant mortality rate and the birth rate can be expected to undergo further adjustments, when the birth of infants who do not survive the first few days of life is registered more accurately than at present.

HOSPITAL SERVICES

The prevalence of serious illness in the African community can be gauged by the statistics of Baragwanath Hospital. The picture is reasonably accurate, because alternative services for this population are very limited and because the urban African mother consents readily to having her child treated in the hospital.

The pediatric division has accommodation for 305 children under the age of 9 years and for 47 of their mothers. For the past 10 years it has been staffed exclusively by African and other "non-white" nurses. Their qualifications are the same as those of white nurses in South Africa, and their efficiency is of a high order. Shortage of accommodation, even for many seriously ill children, has necessitated some departures from conventional hospital organization, and of these the emergency treatment center and the premature baby unit will be referred to in some detail.

MAJOR PEDIATRIC PROBLEMS

In 1959, over 7,000 patients were admitted to the pediatric division; a summary of the major disease groups is shown in Table I. Attendance at the pediatric outpatient department during the same period was 95,000.

Acute diarrheal disorders. In the industrially advanced countries of the world, the epidemiology of diarrheal disorders has un-

Fig. 1. Recently built African townships in the vicinity of Baragwanath Hospital.

dergone considerable change during the past 40 to 50 years. In particular, the summer outbreaks of "enteritis," which killed a large proportion of infants every year, have been eliminated. In the African population of Johannesburg the pattern previously found in the slum areas of the large industrial centers of North America and Europe persists practically unchanged.[2]

The seasonal fluctuations in the incidence of diarrhea are shown in Fig. 3. Attendance at polyclinics, where cases of all grades of severity are treated, is 5 times as high in summer as in winter. The number of children admitted to the hospital, limited to those who are dehydrated, rises nearly 50 times above the winter level. Most of these severe cases occur in children under 2 years of age (80 per cent are under 1 year); 50 per cent suffer from Shigella and Salmonella infections, and 80 per cent show evidence of protein malnutrition.

In malnourished children diarrhea tends to cause hypotonicity of the extracellular body fluids, and for this reason in 25 per cent of our severe cases of diarrhea the serum sodium levels are 125 mEq. per liter or less.[3] Hypertonicity of the extracellular fluids is uncommon in this malnourished population and probably occurs in not more than 5 per cent.[3]

Throughout the summer, our ward accommodation is totally inadequate for the large number of patients in need of intravenous fluid therapy. Admission to the wards is reserved for patients with the worst prognosis, while the others are treated at an emergency center which is attached to the outpatient department (Fig. 4). As a result of this selection, a high proportion of the patients treated for diarrhea in the wards are premature or newborn infants, children in the advanced stages of protein malnutrition, and patients whose body weight is 50 per cent or more below the expected weight for age. Other complicating factors which qualify the patient for admission to the wards are hypertonic dehydration, salicylate intoxication, or lack of response to treatment given in the emergency center.

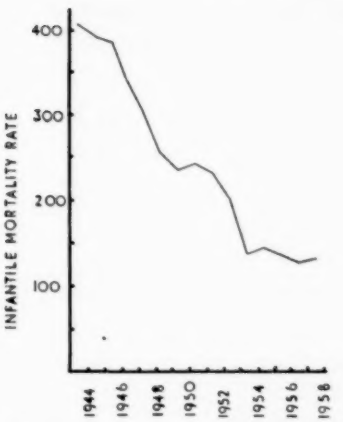

Fig. 2. Infant mortality rate per 1,000 live births of the African population of Johannesburg from 1943/1944 to 1957/1958 (the fallacies of these statistics are discussed in the text).

During 1959, 2,330 children received intravenous fluid therapy in the emergency center, some for periods up to 7 days. The largest number treated in any one month was 575, and the maximum for a 24 hour period was 58. The over-all mortality in the wards and in the center was slightly less than 10 per cent.

Protein malnutrition (kwashiorkor). At birth, African infants in this area have normal serum protein levels, regardless of the nutritional state of the mother.[4] Furthermore, uncomplicated protein malnutrition has never been observed in fully breast-fed infants at this hospital, and no deficiencies have been detected in the breast milk of poorly nourished women.[5]

Through poverty and ignorance, many African infants are weaned on diets consisting mainly or entirely of maize (corn). Within a few months these children usually present the typical features of kwashiorkor, including the characteristic dermatosis. Where wheat or oats have been used instead of maize, the dermatosis does not occur.

Early weaning is often an economic necessity, because it enables the mother to return to work and to supplement the family income. For this reason kwashiorkor is seen at

Table I. Hospital admissions in 1959 (children under 10 years of age)

Medical	
Acute diarrheal disorders	2,734*
Typhoid fever	51
Kwashiorkor	809
Other nutritional diseases	138
Pneumonia	522
Asthma	8
Pulmonary tuberculosis	206
Tuberculous meningitis	54
Acute bacterial meningitis	58
Rheumatic heart disease	52
Congenital heart disease	35
Acute glomerulonephritis	37
Schistosomiasis	23
Prematurity	637
Hemorrhagic disease of the newborn	42
Sclerema neonatorum	38
Accidental poisoning	43
Others (neurological, malignant, metabolic diseases, etc.)	322
Surgical	
Burns and scalds	312
Other conditions	1,737
Total	7,858

*Including admissions to Emergency Treatment Center.

an earlier age in urban than in rural areas; 30 per cent of our advanced cases are under 1 year of age, and less than 20 per cent are over 2 years. Over 50 per cent of those admitted to this hospital with severe manifestations of protein malnutrition have been in the care of relatives or neighbors, in most instances because the mother was away at work. Unfortunately, day crèches, which could play an important part in the prevention of kwashiorkor, rarely admit children under 2 years of age.

There is little evidence that kwashiorkor causes permanent damage. In particular, there is nothing to indicate that it leads to cirrhosis of the liver in this community. The causes and the incidence of cirrhosis of the liver in children admitted to this hospital are essentially the same as in North America where severe protein malnutrition is practically unknown.[6]

The recovery syndrome of kwashiorkor reported from Central America[7] is not seen in this part of Africa. We have, however, observed over 50 children with a neuropathy which occurs exclusively during convalescence from protein malnutrition.[8, 9] Its main features are coarse Parkinsonian tremors and postural abnormalities. Complete recovery takes place within periods ranging from a week to a few months. This syndrome is almost certainly identical with the "acute cerebral tremors" described in Austria in 1909.[10] Even earlier, Rotch[11] in the United States referred briefly to the occurrence of transient tremors in "atrophic" infants. The pathogenesis of this encephalopathy is still obscure.

The case fatality rate of children admitted to this hospital with severe protein malnutrition is 20 per cent. Certain clinical features indicate a poor prognosis.[12] These are: a body weight of 50 per cent or more below normal average; an acute nutritional dermatosis; clinically detectable dehydration, particularly if associated with hyponatremia and hypokalemia; and hypothermia which is usually caused by the muscular weakness or paralysis of hypokalemia. The mortality is also high if there is extreme hepatic steatosis. In some of these cases the serum bilirubin level is slightly raised and, for reasons not clearly understood, this type of patient is prone to sudden and often fatal attacks of hypoglycemia. The latter are usually precipitated by relatively short periods of starvation which would be well tolerated by normal children.[13]

Other nutritional disorders. A diet consisting largely of maize will cause kwashiorkor in infancy, but in children over 3 years of age it will result more commonly in pellagra. Severe hypoalbuminemia, dementia, and diarrhea are rare in our pellagrous patients, and most cases are treated on an outpatient basis because the mortality is low.

Only 4 children with scurvy have been found at this hospital during the past 12 years, despite an intensive search for such cases. This is surprising, because scurvy is not uncommon in adults, and the diet consumed by some pediatric outpatients has a negligible content of vitamin C. The children taking these feeds have normal ascorbic acid blood levels, and the conclusion that

Table II. Weight distribution and survival rate of 3,000 infants admitted to the Baragwanath Premature Baby Unit

Weight-group (pounds)	Number of patients	Deaths		Survival rate (%)
		First 48 hours	After 48 hours	
1-2	166	127	34	3
2-3	721	355	200	23
3-4	1,371	306	163	66
4-5	637	70	35	85
5-5½	71	6	2	89
Incomplete data*	34	29	2	
Total	3,000	893	436	

*Of these infants, 28 were moribund on arrival in hospital.

they are able to synthesize this vitamin appears inescapable.[14]

Rickets is common in this community; it is found in 7 per cent of children admitted for bronchopneumonia. In about 15 patients per year, active rickets is responsible for thoracic cage deformities which are sufficiently severe to cause dyspnea at rest. Re-expansion of the collapsed chest has been achieved in some cases by wire traction on the ribs during intensive vitamin D therapy.

Perinatal problems. In 1959, 7,640 children were born at this hospital and a further 1,642 were admitted to the obstetric division shortly after birth.

In a series of 215 cases of severe neonatal jaundice, only 4 were due to Rh incompatibility.[15] This remarkably low incidence of erythroblastosis fetalis is accounted for by the fact that only 5 per cent of Africans are rhesus negative.[16] Kernicterus occurred, despite exchange transfusions, in 14 of the 215 infants. This complication was caused without exception by "physiologic" hyperbilirubinemia.

Hemorrhagic disease of the newborn has its highest incidence during the late winter and early spring. It is much more common than in white infants. This may be related to nutritional deficiencies in the mother.

Sclerema occurs most commonly in neonates brought to the hospital suffering from gross hypothermia. The prognosis depends on the area of body surface affected by sclerema and is, in our experience, not influenced by treatment with corticosteroids.

An average of 10 infants a year are treated for tetanus neonatorum. They have invariably been delivered at home by relatives or unqualified midwives. The case fatality rate is 75 to 80 per cent, regardless of the method of treatment.[17]

As in the United States,[18] infants weighing 5½ pounds or less at birth are more common in the Negro than in the white population. This can be attributed, at least in part, to suboptimal nutrition of the mothers and to a twin-birth rate which is twice as high as in whites.

In the planning of the Baragwanath Premature Baby Unit the overriding considerations were the very large number of infants to be accommodated and the shortage of staff and lack of equipment. The unit has been described in some detail elsewhere.[19] It now accommodates up to 38 infants and 30 mothers. Infants progress without incubators in a ward which is kept at a

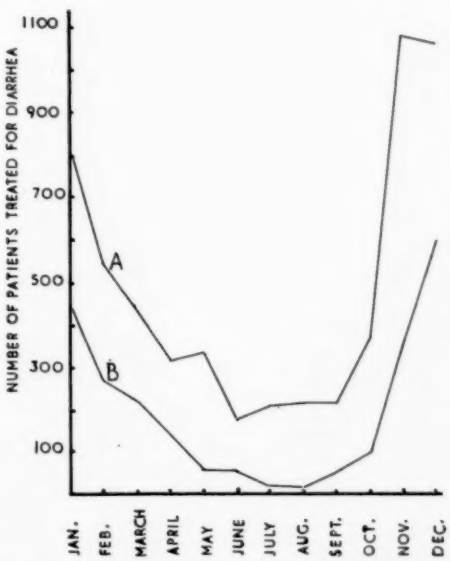

Fig. 3. Seasonal fluctuations in the incidence of acute diarrheal disorders. *A*, Monthly attendance at one of the polyclinics near Baragwanath Hospital. *B*, Children receiving intravenous fluid therapy at the Pediatric Emergency Center.

temperature of 80 to 85° F. by means of coal stoves. Humidity is not controlled. Far-reaching standardization has permitted the employment of mothers for most of the nursing procedures in the ward. Owing to the repetitive nature of the work, the mothers become expert at handling their babies within 2 to 3 days. The nurses act as supervisors and they attend to seriously ill or motherless infants (Fig. 5).

Under existing circumstances, the unit has several advantages over its more orthodox counterparts: the equipment is simple and inexpensive; the ratio of nurses (including mothers) to patients is high; the cross-infection rate is low, because babies are handled by their own mothers only; the training received in the ward enables the mother to take full charge of the baby after leaving the hospital; the great majority of the infants are fully breast fed on discharge from hospital, because the mothers' breasts are stimulated by manual expression or breast-feeding 10 times a day; and the nurses trained in the unit become familiar with a method of premature infant care which can be applied anywhere, even in a primitive environment.

The results obtained in this unit can be gauged from the analysis of the first 3,000 admissions shown in Table II. There were 297 pairs of twins and 17 sets of triplets in this series. Infants weighing more than 4½ pounds at birth were admitted to the unit only if they or their mothers were ill. This explains the high mortality in the weight group of 5 to 5½ pounds.

DISEASES WITH AN UNUSUAL INCIDENCE

Poliomyelitis was, until recently, believed to be less common in African than in white children. A survey indicated that in non-

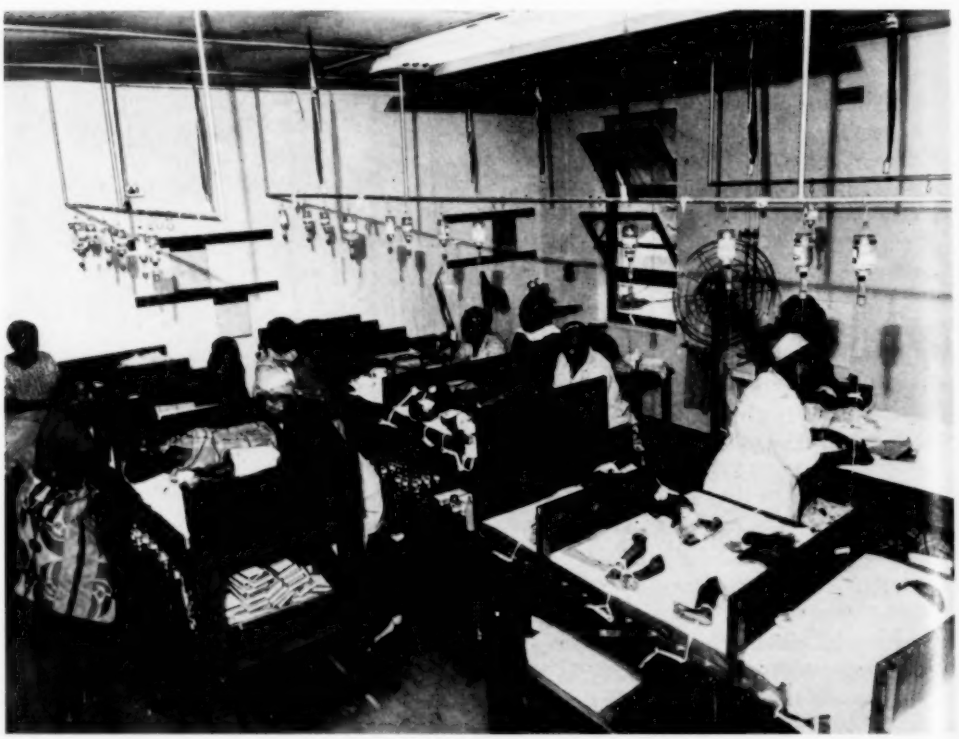

Fig. 4. Emergency Center (infusion needles are fixed to the scalp with plaster of Paris).

epidemic years a considerable percentage of infants became immune to poliomyelitis during the first year of life without developing overt signs of the disease.[20] During an epidemic in 1956, however, African and white children were affected with almost equal severity. As on previous occasions, the age incidence was lower in African children, two thirds of those with paralysis being under 3 years of age.[21]

Rheumatic fever occurs with the same frequency as in white children, but it affects an earlier age group, 15 per cent of patients being under 5 years of age. Our cases of idiopathic cardiac hypertrophy do not differ strikingly from those described in other communities.[22] Furthermore, "nutritional" heart disease, as described by Gillanders[23] at this hospital, has never been diagnosed in a child under 9 years of age. During the past 3 years we have encountered 5 examples of a condition closely resembling "pulseless disease" (Takayashu's disease). The main lesion was a panarterities of the aorta, associated with marked ectasia in 2 of the cases.[24, 25] This disease has not been diagnosed in the white population.

Normochromic,[26] hypochromic,[27] and megaloblastic[28] forms of anemia are common and usually accompany gross nutritional deficiencies or severe infections. A nonthrombocytopenic type of purpura is not infrequently associated with kwashiorkor complicated by tuberculosis or salmonellosis.[29] Acquired hemolytic anemia is rare. In this connection it may be worth mentioning that glutathione instability has been detected in 2 per cent of adult African males.[30]

Of the disorders of the alimentary tract, fibrocystic disease of the pancreas and celiac disease have never been observed and congenital pyloric stenosis is exceedingly rare.[31]

Fig. 5. The premature baby unit at feeding time.

We see only about 3 examples of acute appendicitis annually; this condition has, therefore, about the same incidence as perforated typhoid ulcer.

Allergic conditions such as asthma and infantile eczema are uncommon in African children.

Some orthopedic conditions are also uncommon in the African child. No case of congenital dislocation of the hip or osteochondritis was seen at this hospital during one period of 4 years. For comparison, there were over the same period 42 admissions for congenital dislocation of the hip and 30 for osteochondritis to the Transvaal Memorial Hospital for Children, an institution serving the white population of Johannesburg.[32]

Malignant diseases have a lower incidence in African children than in white children.[33] Acute leukemia is of great rarity and usually not more than 2 to 3 cases are diagnosed annually.

DISCUSSION

The main pediatric problems in the African population of Johannesburg are strikingly similar to those encountered in the working class of the world's largest industrial centers during the early part of this century. At that time an infantile mortality rate of 200 or more per 1,000 live births was not unusual. In the United States it was highest among Negroes "and in no other race [were] there so many married women at work in factory and field."[34] During the past 30 to 40 years higher standards of education, better living conditions, and more effective public health services have lowered the infant mortality in many of the large cities of Europe and America to below 30 per 1,000 live births.

Unfortunately, the child health services, limited as they are in this region, do not yet have the same appeal for most African mothers as the curative services. Attendance at child welfare clinics indicates that it requires a considerable degree of literacy and sophistication to recognize the advantages of preventive medicine. Already tremendous progress has been made in housing and sanitation. Increasing literacy and adaptation to urban living conditions will undoubtedly bring further advances.

In the remainder of Africa important political and economic developments are at present taking place, and there are indications that large industrial centers will arise in many areas. With a well-planned educational and preventive medical program it should be possible to avoid the wastage of child life which, traditionally, accompanies the change-over from an agrarian to an industrial economy. Success in this direction, however, will be limited by the extent to which women who have grown up in a primitive environment can be led to practice birth control and to accept modern methods of child care.

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MEDICAL PROGRESS

Some newly described viruses and diseases associated with them

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WHEN virology is surveyed from the vantage point of the beginning of the sixth decade of the twentieth century, the recent great increase in the number of recognized viruses is striking. From 1898 to 1948, 60 viruses were described. By 1959, the number had increased to 200.[1] This recent increase reflects many factors, but perhaps mostly the availability of pure cell line tissue cultures and antibiotics for virus isolation. Many of these viruses are still "in search of diseases." Despite this large number of "available" viruses, the majority of human infections which are labeled clinically as "probably viral in origin" are still unidentified etiologically.

The surveyor is also impressed by the observation that a single virus might produce multiple clinical syndromes depending upon the age or state of the host. Thus, the rubella virus in the fetus leads to cardiac, ocular and otitic malformation and even death[2]; in childhood it produces a mild exanthem, and in adulthood this exanthem is frequently complicated by arthritis. Similarly, the virus of herpes simplex in the newborn often causes a severe illness with hepatitis,[3] central nervous system involvement,[4] and even death, often without skin manifestations; in childhood it produces mouth, throat, and skin vesicles and ulcers, usually with fever; and in adulthood it is associated with recurrent aphthous ulcers, "cold sores," without fever. The cytomegalic inclusion disease viruses cause hepatitis and brain damage to the fetus[5] and no obvious disease in the adult. Coxsackie B viruses are responsible for instances of myocarditis and encephalitis in the newborn, and in the adult characteristically lead only to pleurodynia or aseptic meningitis.[6] Chicken pox virus produces a typical exanthem in childhood, and in the adult, who has had chicken pox, it becomes clinically apparent as herpes zoster.[7]

Conversely, this same surveyor is impressed by the observation that single clinical syndromes may be caused by many different viruses—probably because there are

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limited ways cells may react. Thus, clinical "croup" has been associated with the influenza[8] and para influenza viruses.[9, 10] Similarly, "aseptic meningitis"[11] or even paralytic disease with meningitis has been caused by the poliomyelitis, ECHO,[12] Coxsackie[12] and mumps[13] viruses.

If the surveyor happens to be a pediatrician, he might ask himself some rhetoric questions: Why is it important for pediatricians to know that they are dealing with a viral disease? What difference does it make whether we know that a particular virus is responsible for a patient's illness? The answers are both philosophical and practical. Philosophically, man has always wanted and needed to know his antagonists. Before the age of science, he created magic and evil spirits to account for many of the ills he could not otherwise understand. Practically, once we recognize our antagonist we can predict from our knowledge of his previous behavior how he will act. Thus, we can prepare ourselves, the patient, and his family for what lies ahead. (One of the great satisfactions of pediatrics is to be able to predict what will happen to a child with roseola.) When we know with what virus we are dealing, we can often anticipate our therapeutic approach, and from our previous knowledge of its means of spread attempt to contain it within reasonable bounds. For example, if we knew that we were dealing with eastern equine rather than mumps encephalitis, our handling of the isolation of the patient and his environment would be quite different. The former requires no isolation but an intensive antimosquito campaign, the latter only isolation of the patient.

Among the newly discovered viruses with associated diseases which are of pediatric interest are the enteroviruses (polio, ECHO, and Coxsackie), the adenoviruses, the para influenza and cytomegalic inclusion disease viruses.

More than 50 viruses have been identified in the enterovirus or P. E. C. (polio, ECHO, Coxsackie) group. These viruses are grouped together because they are all recovered from stool, are all small, and have epidemiologic and clinical features in common. Their differentiation is based upon laboratory study, chiefly of cytopathogenicity for HeLa (a human cancer cell) and monkey kidney cells in tissue culture, and pathogenicity for monkeys and suckling mice.[14] Thus, in general, only the 3 polio virus types produce disease in monkeys and cell changes in both HeLa and monkey kidney tissue cultures; the 19 Coxsackie A types and 5 Coxsackie B types produce disease in suckling mice but not in monkeys, and only the B types uniformly produce changes in monkey kidney cell tissue cultures; the 24 ECHO types fail to produce disease in either monkeys or suckling mice but do produce cytopathogenic effects in monkey kidney cell tissue cultures, not in HeLa cells. The cytopathogenic changes produced in monkey kidney cell cultures by polio, Coxsackie B, and ECHO viruses are distinctive, and each can also be recognized by the plaque it forms.[15]

There are exceptions to these generalizations and they should not be taken too rigidly. Thus, Coxsackie A-7 (Russian "Type IV polio virus") does produce paralysis in monkeys,[16] a few Coxsackie strains do well in HeLa cell cultures, and ECHO 9′ produces disease in suckling mice.[14]

The clinical syndromes associated with the polio viruses are well known. However, it is well to recall that Salk vaccination does not prevent intestinal infection. In vaccinated patients polio virus may multiply in the bowel, and yet not get into the central nervous system.[17] Feeding attenuated strains of polio, as with the Sabin vaccine, raises the problem of recognizing these viruses when a polio virus is recovered from the stools of an ill patient. Monkey inoculation is difficult and expensive. Fortunately, there are indications that "wild" or "street" polio virus can be differentiated from attenuated strains quite simply by using physical "markers" such as difference in heat stability and elution from cellulose columns.[18]

Coxsackie Group A viruses which produce a generalized myositis in suckling mice have been associated clinically with herpangina.[19] This acute febrile summer illness is char-

acterized by sore throat and the appearance of minute vesicles and small ulcers on the anterior tonsillar pillars, tonsils, or pharynx. Although the symptoms clear in a few days, the lesions may persist for much longer. The immunity is type specific, so that recovery from an infection with one type does not protect against infection with another. A-16 has recently been recovered during a summer outbreak in Canada of febrile illness with ulcerating lesions of the mouth and a vesicular rash.[20]

These A viruses may also play a role in potentiating weak strains of polio as suggested recently by Steigman.[21]

Coxsackie Group B viruses, which produce scattered focal lesions of muscles, central nervous system, and fat pads in suckling mice, have been associated with at least 3 clinical syndromes in humans.[6] They are: (1) Epidemic pleurodynia (Bornholm's disease or "devil's grippe"); (2) aseptic meningitis (where the virus is rather readily recovered from cerebrospinal fluid, unlike polio); and, in infants who are usually infected in utero; (3) acute aseptic myocarditis and meningoencephalitis (which is characterized by the sudden appearance of fever, tachycardia, tachypnea, vomiting, convulsions, and death).

Dalldorf[22] has suggested on epidemiologic grounds that Coxsackie B virus may interfere with infection by polio virus. When and where there is a high incidence of Coxsackie B disease, polio incidence is very low.

ECHO (enteric, cytopathogenic, human, orphan) viruses have been associated with at least 8 clinical syndromes[15] most of which are quite nonspecific except when the rash is present. They are: (1) aseptic meningitis, (2) aseptic meningitis with a rash, (3) mild paralytic disease, (4) "summer grippe," (5) "summer grippe" with rash, (6) Boston exanthem, (7) summer diarrhea in infants and children, and (8) mild upper respiratory and gastrointestinal symptoms.

Most of the types of ECHO are potentially capable of producing any or all of these syndromes, although certain types have been more frequently associated with some of them. In any one outbreak, a single type may produce a variety of symptoms. However, 4 and 9 often cause rashes, 9 has been responsible for several large epidemics of aseptic meningitis, and so far only 16 has been associated with Boston exanthem.

The rash of ECHO disease[14] is usually rubelliform with pink to violaceous macules appearing first on the cheeks and spreading within a few hours to the trunk. It usually appears early in association with the fever (except with Type 16 or Boston exanthem when it occurs later). It fades in 3 to 5 days. Occasionally it may be scarlatiniform or petechial and has even been confused with the rash of meningococcemia. The rashes seem to occur more frequently in young children.

The adenoviruses are primarily respiratory tract viruses which were discovered by the use of roller tube tissue cultures, in which they produce cytopathogenic effects.[23] Like most of the ECHO viruses, man is the only susceptible animal. There are now at least 19 distinct serologic types differentiated by neutralization tests. However, all adenoviruses share a common complement fixing antigen, and this is useful in differentiating them from ECHO strains, since adenoviruses may also be found in stools. Another differentiating point is that adenoviruses do well in HeLa cell cultures and poorly in monkey kidney cell cultures, while ECHO strains do the reverse, i.e., do well in monkey kidney cultures and poorly in HeLa cells. All adenoviruses, except Types 12 and 18, show the hemagglutination and hemadsorption phenomena,[24] and in this respect they resemble the myxoviruses.

At least 6 clinical syndromes have been consistently associated with adenoviruses.[23] They are: (1) acute febrile pharyngitis with or without other upper respiratory symptoms. This is probably the most frequent manifestation. It is endemic in children and usually noted in the winter months (Types 1, 2, 3, and 5). (2) Pharyngoconjunctival fever is a summer epidemic disease, also of children, with temperatures to 103° F.,

mild sore throat, conjunctivitis, headache, and listlessness (Types 3, 7, and 14). (3) Acute respiratory disease (ARD) is epidemic in young recruits—fever, chills, and headache with other respiratory symptoms (Types 4 and 7). (4) Pneumonia, also epidemic in young recruits, like primary atypical pneumonia, although cold agglutinins are absent. There is one report of a hospital outbreak in Paris involving 20 infants of whom 8 died. At postmortem, intranuclear inclusion body pneumonia was found (Types 4 and 7). (5) Acute follicular conjunctivitis, endemic in adults, usually without fever and often monocular (Types 3, 6, and 2). (6) Epidemic keratoconjunctivitis, epidemic in adults who are exposed to corneal trauma (e.g., shipyard workers) (Type 8).

Although respiratory infections due to adenoviruses have a high incidence in military recruits, they are not responsible for very much clinical illness in civilian populations.[25, 26]

There are at least 8 myxoviruses. These have all been recovered from the respiratory tract, are all medium in size, and all react with certain mucins in erythrocytes (hence the term "myxo") and show hemagglutination or hemadsorption. They are: Influenza A (also A′ and A″), Influenza B, Influenza C,[27] Newcastle Disease Virus, mumps, para influenza virus Type I (Hemadsorption II, Sendai, or Influenza D), para influenza Type II (croup associated virus), and para influenza Type III (Hemadsorption I).[28]

The para influenza viruses were also discovered as a result of the use of tissue culture. Virus is grown in cells in roller tubes and, before any pathogenic effect is visible, monkey or guinea pig red blood cells are added, and the pattern of their sticking to tissue cells is noted. This is called "hemadsorption." At least 3 serologically specific viruses have been uncovered with this technique. Identification is by hemadsorption-inhibition tests and by cytopathogenic effect produced.[10]

Any type of respiratory illness may be produced by any of these para influenza viruses, and their prevalence varies from year to year in any one location. In 1957 to 1958 in Washington, D. C., among 1,738 children in hospitals because of respiratory illnesses, Types I and III together accounted for about 20 per cent of the illnesses.[29] Type II which was recovered from outbreaks of croup in Cincinnati and Toronto in 1955 could not be recovered by the same investigators from croup patients in those cities the following year.[9]

The cytomegalic inclusion disease viruses (human salivary gland viruses) were recovered as the result of the use of tissue culture techniques employing human cells. They are species specific. There are now apparently several viruses which are antigenically unrelated which may be responsible for human infection.

The infection in adults is usually asymptomatic, and cytopathology is discovered accidentally at postmortem. However, in young babies it can produce serious illness. A recent review of 12 virologically proved instances by Weller, Hanshaw, and Scott[5] revealed the following common clinical features: hepatosplenomegaly in all, jaundice in 10 of the 12, mental retardation and microcephaly in 7 of the 12, chorioretinitis in 4, petechiae in 5, and periventricular cerebral calcification in 3.

They found that infected infants might continue to excrete virus in the urine for months and years even after the development of neutralizing antibodies, and that they might recover virus in the urine, and not find the typical cytomegalic inclusion cells in the urinary sediment.

The disease in the newborn is the result of an intrauterine infection. Since the mother is usually asymptomatic, it is thought that some unknown factor, perhaps pregnancy itself, activates a latent virus. If this is so, subsequent pregnancies might also be subject to this same risk unless the mother becomes free of the virus or unless some fetuses are less susceptible than others. It may also be that the infant only becomes infected if the mother has an acute infection, as with toxoplasmosis. Whatever the cause, when the few reports of subsequent pregnancies

in women who had been delivered of infants with cytomegalic inclusion disease are examined, it seems that the prognosis for future pregnancies is good. Such an instance was recently published by Potter.[30]

The number of recognized viruses which are associated with human diseases has become so large that one must look for unifying principles. In this review it has been shown that there are clinical, epidemiologic, and laboratory reasons for grouping viruses as enteroviruses, adenoviruses, myxoviruses, or cytomegalic inclusion disease viruses. However, it has been emphasized that the same virus may produce a variety of clinical syndromes, and conversely that the same clinical syndrome may be produced by a variety of different viruses. For the pediatrician, this is one of the most important lessons learned from the more frequent application of virologic techniques to clinical material.

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CLINICAL PATHOLOGICAL CONFERENCE

THE CHILDREN'S HOSPITAL MEDICAL CENTER, BOSTON, MASS.

Sidney Farber, M.D., Editor
Gordon F. Vawter, M.D., Assistant Editor

THIS 4-year-old girl was transferred to The Children's Hospital Medical Center from another hospital because of fever and convulsions.

The family history is negative apart from a paternal grandfather with recently discovered diabetes mellitus, treated by diet. The parents and a 6-year-old sibling are well.

The past history indicates that the birth weight was 8 pounds, 12 ounces, and that the term birth and the neonatal and development history were entirely normal. Usual immunizations had been given and she had measles when 2 years old.

Four days prior to admission, a croupy cough subsided with cough syrup and one adult aspirin tablet. She continued afebrile, but 2 days later vomited once and on the next day vomited all oral intake. She became drowsy and awoke that night screaming and disoriented. She was admitted to another hospital at 1:00 A.M., with a temperature of 99.6° F. On admission she was given orange juice and Karo syrup. Penicillin and streptomycin were begun. At 5:00 A.M., 4 plus urinary reducing substance was noted; blood was drawn for sugar determination; and 10 units of insulin was given. Over the next 12 hours an additional 25 units of insulin was given by clysis in 5 per cent dextrose in water. At 7:00 A.M. the blood sugar on the previously drawn sample was reported as 105 mg. per cent. Blood nonprotein nitrogen was 28 mg. per cent, and leukocytes were 10,900 per cubic millimeter. Her temperature rose to 104 to 105.8° F., tonic and clonic jerks of both upper extremities developed, and she became comatose. She entered The Children's Hospital Medical Center at 3:30 P.M. the same day.

Examination here showed: temperature 104.6° F., pulse rate 160 per minute and regular, respirations 60 per minute and stertorous, and blood pressure 120/70 mm. Hg. She was well developed and nourished, with hot flushed skin. The head was normal. Ears, nose, throat, heart, and lungs were normal. The neck was not stiff. She was comatose with conjugate gaze—eyes reacting to light and vestibular stimulation. Gag and corneal reflexes were elicited. Babinski tests were positive, bilaterally. No other reflex activity was found.

Urine, obtained via indwelling catheter, demonstrated pH 6.0; specific gravity 1.025;

albumin 300 mg. per cent; sugar negative; acetone 1 plus; erythrocytes 200; and coproporphyrins qualitatively negative. Blood contained hemoglobin, 16 Gm. per cent; leukocytes, 5,500 per cubic millimeter, with 58 per cent polymorphonuclear leukocytes, 24 per cent band forms, 16 per cent lymphocytes, and 2 per cent monocytes. There were abundant platelets and no basophilic stippling. Blood and cerebrospinal fluid cultures were negative. Nose and throat culture grew a few *Staphylococcus aureus* organisms. Spinal fluid showed 250 mm. pressure, 48 mg. per cent sugar, 14 mg. per cent protein, 2 polymorphonuclear leukocytes, and 1 monocyte. Blood contained nonprotein nitrogen 40 mg. per cent; sugar 40 mg. per cent; pH 7.5; carbon dioxide 18.1 mEq. per liter; potassium 4.7 mEq. per liter; chloride 111 mEq. per liter; calcium 11.5 mg. per cent; and phosphorus 3 mg. per cent.

Fifty millimeters of 50 per cent glucose was given twice intravenously when the blood sugar determination was reported, but there was no dramatic change in the patient's condition. Laryngeal stridor developed and she was placed in a respirator after endotracheal intubation. Generalized clonic seizures beginning on the left were controlled with Amytal and ice packs. Blood pressure fell, despite Levophed and Solu-Cortef. Antibiotics and aspirin were also continued.

She died approximately 20 hours after admission.

DR. WILLIAM BERENBERG.* I would like to believe the special applicability in this patient of something frequently emphasized, namely, that careful history taking is often more important than much of the data we may obtain by laboratory means. Starting with an individual who has been relatively well, but then goes on to develop a respiratory infection complicated by severe vomiting and progressing to a state of disorientation with coma and convulsions, we have depicted a fairly typical history for a clinical picture of encephalitis. The preceding respiratory infection raises the possibility of direct cerebral infection, possibly viral, but there is no supporting evidence for this in examination of the cerebrospinal fluid where cellular response might be expected. One should consider a postinfectious encephalopathy which, although predominantly a white matter disease and usually occurring somewhat later, should ordinarily be associated with at least some elevation in cerebrospinal fluid protein, if nothing else. The absence of external evidence of bruising and the absence of localizing symptoms argue against the diagnoses of trauma or neoplasm. The sudden onset of vomiting followed by encephalitic manifestations in a child this age should raise the question of exogenous or accidental ingestion of toxic agents, such as lead, insecticides, thallium, and the like. These may be rather difficult to find and to prove, even when searched for carefully.

The negative urinary coproporphyrin, together with the absence of cerebrospinal fluid protein abnormality and the lack of stippling of red cells, certainly argues strongly against all but the most acute varieties of lead poisoning. Similarly, the lack of alopecia and severe gastroenteritis would exclude chronic thallium intoxication, which otherwise would fit much of this picture quite well.

There are many questions which evolve with relation to the previously demonstrated glycosuria. In evaluating the demonstration of urinary reducing substances, one should consider possible errors in technique, problems arising from short-cut diagnostic tests which may lack specificity, the possibility of pentose, salicylates, streptomycin, and other substances which may contribute to the determination of total reducing substance. We must assume, having excluded these, as those who treated this child did, that one is dealing with glucose. With the family history of diabetes and the heavy birth weight, there is a natural suspicion of the potentiality for development of diabetes. Against this diagnosis are perhaps, the pre-

*Assistant Clinical Professor of Pediatrics, Harvard Medical School, and Chief of Infants and Medical Division, The Children's Hospital Medical Center, Boston, Mass.

vious good health, the lack of specific diabetic symptoms, and particularly the fact that no ketone bodies are described in the urine. One could attempt to explain the glycosuria on the basis of ingestion of carbohydrates after a presumed period of depletion due to fasting. We must consider the knowledge that various encephalopathies and convulsive states may be associated with otherwise unexplained and usually transient aberrations of glucose metabolism. We also must remember that intoxications, particularly those occurring with the ingestion of lead or of dinitrophenol, may manifest reducing substance in the urine. In the experimental animal the shocklike states following the generalized Schwartzman phenomenon and the intravenous injection of endotoxin from gram-negative bacteria may be associated with marked hyperglycemia. The other noted abnormalities in this patient's urine should make us consider a specific renal disease, such as glomerulonephritis, specific renal tubular dysfunction (acquired or congenital as seen in Fanconi's syndrome or in Lowe's syndrome), or even renal vein thrombosis. There is no conclusive evidence for any of these, although I doubt that aminoaciduria was excluded. The hematuria and proteinuria remain unexplained problems unless, as I expect, they may be the result of the trauma of catheterization.

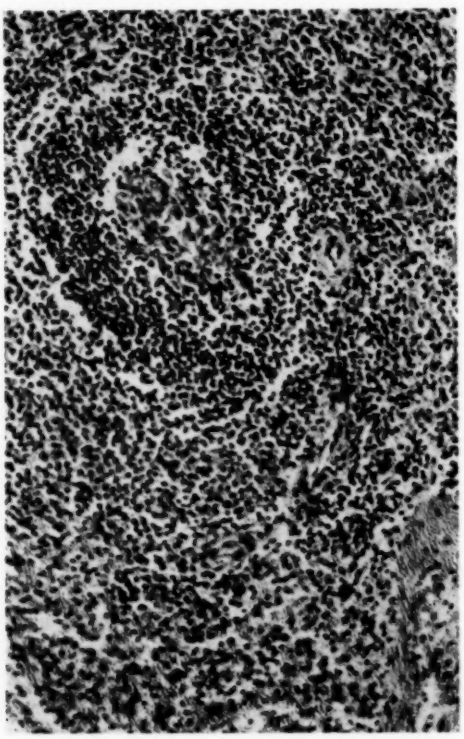

Fig. 1. Spleen. White pulp has indistinct margins, resulting from lymphocytic encroachment upon red pulp. There is no chromatin debris in the germinal center. (Hematoxylin and eosin. ×140.)

DR. SHERWIN V. KEVY. Gross hematuria was not noted prior to the insertion of the indwelling catheter.

DR. BERENBERG. One wonders next about the effects of the insulin which was given to this child. If she were truly diabetic, I would expect the dosage was appropriate and safe. However, I am not so sure about this dosage in a child who has presumably been fasting as a result of vomiting, and who does not have the full-blown metabolic aberration of diabetes. In fact, about the time the insulin was given, the blood sugar was 107 mg. per cent, and it was after the administration of insulin that the temperature rose and convulsions appeared. Could these be hypoglycemic responses as suggested by the blood sugar determination obtained after admission here? If so, we may assume that this is not all that is wrong and should suspect that more than one disease process may be at work since there was no response to 50 per cent glucose administered intravenously on arrival. Moreover, this treatment might be expected to have some beneficial, if transient, effect upon cerebral edema. The fact that there was no change in the clinical state indicates that there are complicating factors or that the cerebral insult is more specific. The assumption that there exists more than simple cerebral edema leads me to three principal considerations of the nature of the primary process: (1) A direct viral encephalitis

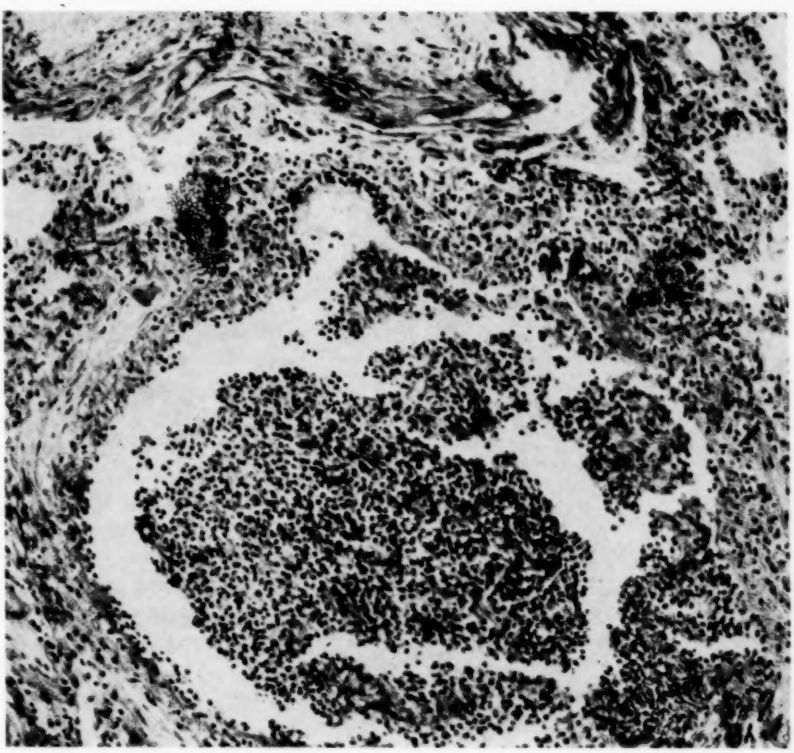

Fig. 2. Lung. Necrotizing bronchitis is conspicuous. Epithelium has been lost. Leukocytic infiltrate is mixed. (Hematoxylin and eosin. ×190.)

could explain much of this entire picture, although, in general, one would expect that with a viral encephalitis which was this overwhelming, we should have encountered some cellular response in the spinal fluid. (2) In a so-called postinfectious encephalitic state major lesions are in white matter and often go on to a demyelinating state. These changes are unlike the direct viral encephalitic lesion which is more often cortical and involves principally gray matter. Similar pathologic states may also occur with other toxic and bacterial diseases. (3) For reasons already touched upon, I cannot exclude any number of possible intoxications or ingestion of various poisons. Certainly the ingestion of some insecticide could fit this picture as well as any other diagnostic possibility, although we have no direct evidence of this.

Almost certainly there will be some element of pneumonia found in this child's lungs.

DR. SIDNEY FARBER. If you had seen this child yourself, what would have been your course of action?

DR. BERENBERG. Probably I would have managed the patient very much the way she was handled after admission to this hospital, although perhaps I would have made a more vigorous attempt to obtain some history of poisoning and searched for some of the specific poisons mentioned above in the urine. I might have given serious consideration to the treatment of the cerebral state by the use of hypertonic solutions.

DR. RANDOLPH K. BYERS. I would agree with Dr. Berenberg that if one did not know all we know about this patient, one

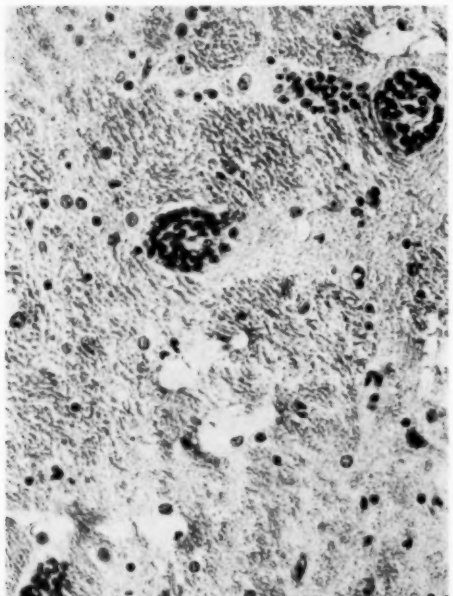

Fig. 3. Brain. Round cells from cuffs around small blood vessels. Reactive changes in glia are mild and early. (Hematoxylin and eosin. ×150.)

would certainly be satisfied to think this an instance of acute toxic encephalopathy which may have one of many possible causes. Most of you know a man who works around the hospital who entered here as a child with just such a clinical picture, with a quite benign-appearing throat, but who had a blood stream full of streptococci. He came around quite rapidly with intravenous sulfonamides. It may well be that the antibiotic treatment which the present patient received at the referring hospital was just the thing to do at that moment, but it served also to obscure the real state of things when she came here. I would prefer to withhold insulin in the dosage used until I knew what the blood sugar was, unless the clinical state or laboratory data suggested ketosis.

I should like to make one point about acute lead poisoning, that infection sometimes seems to uncover or precipitate an acute symptomatic plumbism. I have seen chickenpox do this, for instance.

Dr. Charles A. Janeway. I am a little worried about the possibility of aspirin poisoning in this case. Much of what is described here would fit quite well.

Dr. Kevy. She received a total of 4 doses of 240 mg. of aspirin, so far as we know, both here and at the referring hospital.

I wonder if Dr. Crigler would comment upon the fact that this youngster received her insulin about 10 hours before admission here at which time her blood contained 40 mg. per cent of glucose. How likely is the deterioration she suffered just prior to admission here related to possible hypoglycemia?

Dr. John F. Crigler. It is true that on the average, the maximum hypoglycemic effects following regular insulin occur somewhere between 3 and 8 hours after administration. The variability stems from many factors which include availability of carbohydrate, general metabolic activity, and rate of absorption of the insulin; all, in turn, depend upon the circulatory state. Although one cannot reconstruct this in detail, it would be difficult to exclude the possibility that insulin hypoglycemia played a definite role in this case; prolonged hypoglycemia, in itself, can lead to cerebral swelling.

Dr. Byers. Those who have worked with insulin shock in the treatment of psychosis give a pretty clear picture of what I call "quiet decerebration" in their patients, and while they may have convulsions for a while, they later become unconscious and are very relaxed and hypotonic, with brain stem phenomena, terminally, if the process goes too far. I suspect that something more violent or active affected this child's brain as indicated by the tachypnea, hypertension, glycosuria, activity state, and so on.

Dr. Kevy. The house staff diagnosis was viral encephalitis.

Dr. Farber. Dr. Vawter, would you give the findings?

Dr. Vawter. We can list a number of findings and detail some additional diag-

nostic studies, but cannot offer an absolute diagnosis. There were no signs of chronic wasting illness, such as might occur with a metabolic or nutritional defect. Reactive changes in lymphoid tissue suggest that the basic process was an inflammatory one of 72 to 96 hours' duration (Fig. 1). There was a well-established necrotizing and ulcerative tracheitis which could, by its appearance, antedate the intubation and probably is related to the development of laryngeal stridor which prompted tracheotomy. The mononuclear character of the infiltrate also raises the question of possible viral origin. This process extends down along bronchi when, as predicted, there are areas of lobular pneumonia as well (Fig. 2). Our postmortem bacterial cultures of blood and lung were sterile and Dr. Kibrick's attempts at isolation of a virus on tissue cultures of human amnion and human kidney were also negative; his studies however, would not have excluded herpetic or influenzal viruses. There were no renal lesions of note and petechial hemorrhages were found in the bladder neck, probably traumatic in origin. The brain was considerably swollen and weighed 200 grams more than expected for this age, but no other gross abnormality was seen. Microscopically, much of the cerebral tissue appeared quite bland, as one might find in toxic swelling or encephalopathy. Focally, however, especially in and around brain-stem structures, there were well-defined perivascular cuffs of mononuclear cells and polymorphonuclear leukocytes. At the simplest level these are presumptive evidence for vascular damage (Fig. 3) Although direct degeneration of neurons did not accompany these lesions, it might be too early to see it, just as it is too early to expect these changes on a basis of so-called postinfectious encephalopathy on the basis of clinical data. In summary, the evidence points to an *unidentified viral infection,* with involvement of the respiratory tract and with an *encephalitis,* also probably viral. An element of toxic encephalopathy exists also. The possible pathogenic roles of the various events of the clinical course (such as possible hypoglycemia) continue to be speculative.

COMMENTS ON CURRENT LITERATURE

Antihemophilic globulin levels in carriers of hemophilia A

DEVELOPMENTS within recent years have shown that prolonged coagulation time may indicate deficiency in any of several substances necessary for thromboplastin activity. In consequence, the concept of hemophilia as a readily definable clinical entity has undergone modification. The major substances essential for thromboplastic activity include antihemophilic globulin (AHG, thromboplastinogen, plasma thromboplastin factor), plasma thromboplastin component (PTC), and plasma thromboplastin antecedent (PTA). The hemorrhagic conditions associated with these deficiencies are now recognized as distinct clinical entities, and their classification into hemophilias A, B, and C, respectively, is generally accepted at the present time.

Hemophilia A, the so-called classic hemophilia, is inherited as a sex-linked recessive. Typically, clinical manifestations occur in affected male progeny, and the trait is carried as an inapparent genetic character by the heterozygous female (carrier). Rarely, the condition may occur in females who are homozygous, resulting from those infrequent instances in which an affected male has married a carrier female, as in some consanguineous marriages in isolated communities, or conceivably by the occurrence of mutation. The person with true hemophilia is unable to produce AHG in adequate quantity. Clinical manifestations may be evident very early in life, as bleeding from the cord or following circumcision, or the condition may not be apparent until the child is old enough to experience trauma, loss of teeth, etc. In severe cases hemarthrosis with attendant sequelae is a characteristic finding and may appear as soon as the infant begins to walk. Bleeding in hemophilia may involve the viscera or the central nervous system. Prothrombin time and bleeding time are normal while the thromboplastin generation test reveals a deficiency of antihemophilic globulin with inadequate activity of thromboplastin. Differential diagnosis in hemophilia A can be made by the so-called "mixing" tests, various combinations of fresh normal blood or plasma, and known hemophilic blood or plasma, as indicated. Families have been recorded in which a mild form of true hemophilia occurred in male members, caused apparently by partial lack of AHG. This observation has been interpreted genetically as possible evidence that the X-chromosome recessive factor may be variable in its expression, or that its expression might be influenced by other factors present in the genetic complex.

The potential carrier female presents a problem and, ever since the first genealogy of hemophilia was described[1] in the Appleton-Swain family in 1813, many attempts have been made to demonstrate some degree of abnormal coagulation in the female which might identify the carrier. These attempts have included the use of clotting

time determinations, thromboplastin generation tests, prothrombin consumption, plasma recalcification tests, and AHG assays. Some of the earlier investigations were summarized by Nilsson and his associates[2] in 1959 in a review made in connection with laboratory studies, employing chiefly plasma recalcification time under controlled conditions. From their own results in 28 definite or possible carriers of hemophilia A and those of other investigators these authors concluded that the majority of female carriers have lower than normal levels of AHG. About the same time, Pitney and Arnold[3] employed a sensitive modification of the thromboplastin generation test to detect mild deficiencies of AHG in female carriers, emphasizing that a very sensitive AHG assay method is required to distinguish carriers.

Two recent reports are of special interest. The *Journal of Laboratory and Clinical Medicine* for October, 1960, carries a report by Bentley and Krivit.[4] By the use of a modification of Quick's[5] erythrocytin assay for antihemophilic globulin, 21 definite carriers and 5 probable carriers were studied for plasma AHG levels. Twenty-three of the 26 women studied "showed abnormally low AHG levels (30 to 40 per cent) in the range between those found in normal persons and in patients with hemophilia."[4] It seemed evident to these investigators that female carriers of classic hemophilia are manifesting the presence of one abnormal X-chromosome gene by a lowered plasma AHG level. In family studies, similar levels of AHG were observed in siblings and in different generations of the same family which suggests "that the exact plasma level of AHG is evidently a genetically controlled factor."[4] Five of the mothers studied had a history of minor bleeding tendencies associated with surgical procedures, and 22 of the 26 stated that they had experienced easy bruising all their lives. While the mechanism of the reaction is not understood thoroughly as yet, the erythrocytin test for detecting differences in AHG level was found by these authors to be an extremely sensitive one. In one case a very slight deficiency detected in the mother was verified by birth of a son with typical classic hemophilia.

The second of these reports is by Rapaport, Patch, and Moore,[5] and appears in the November, 1960, issue of the *Journal of Clinical Investigation*. Rapaport and his coworkers have been interested for several years in the various methods available for the detection and measurement of antihemophilic globulin and have studied in detail the Pool and Robinson[6] modifications of the thromboplastin generation test. The present report[5] concerns quantitative measurements of AHG made by various methods, with particular reference to the Pool-Robinson technique. Thirty-five obligatory carriers and 30 normal women were studied. The obligatory carriers included (1) daughters of known hemophiliacs, (2) mothers of 2 or more hemophilic sons, and (3) mothers of 1 hemophilic son who had at least 1 other close male relative with hemophilia. The normal women were selected from personnel in the medical school, secretaries, technicians, etc., with no personal or family history of abnormal bleeding. The normal women had a mean AHG value of 92 per cent of the reference plasma employed, while the carrier women had a value of 58 per cent. One obligatory carrier with 22 per cent AHG had experienced clinically significant bleeding. Seven carriers with AHG levels between 30 and 40 per cent had had no bleeding tendencies. On the basis of their results, the authors suggest that AHG levels low enough to predispose to bleeding (below 30 per cent) can be expected in about 20 carriers per 1,000. Probability calculations indicated that the AHG assay employed "will detect with reasonable accuracy (four chances out of five) about 75 per cent of the true carriers in a potential carrier population, and about 66 per cent of the normal members in a potential carrier population. However, a potential carrier with a high AHG level still retains one chance in five of being a true carrier."[5] While in general the several techniques available for the measurements of AHG give

comparable results and are considered adequate for practical purposes, these authors encountered certain differences which may result in higher values of AHG in carriers but not in normal subjects and are of the opinion that this aspect of the problem needs clarification. Bentley and Krivit[4] found the erythrocytin test for determining AHG levels to be extremely sensitive as shown by the ease with which small differences in the AHG levels could be detected and by the reproducibility of the results. The investigations which are being continued in this field will be of considerable interest and are of importance from several points of view: the mechanism of the reaction and the biologic systems involved, the genetic complex concerned, and differentiation of the forms of hemophilia from the clinical viewpoint.

Tests such as these designed to detect carrier states are of paramount importance in the general field of genetics and may open the way for some degree of control of genetically determined maladies.

RUSSELL J. BLATTNER, M.D.

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News and notes

The **Association for Pediatric Ambulatory Service,** formerly the Association of Pediatric Out-Patient Directors, was organized in Chicago Oct. 18, 1960, to promote improved patient care, teaching, and research in ambulatory pediatrics. It is independent and unaffiliated with any other pediatric organization. Charter members have interests and activities for the most part concerned with outpatient department functions. Membership is open, upon application, to others interested in various aspects of ambulatory pediatrics.

An annual meeting will be held in conjunction with the spring meetings of the American Pediatric Society and the Society for Pediatric Research and will consist of an open scientific program of papers dealing with teaching, patient care, and research in pediatric problems in ambulatory patients and a business meeting for members.

For further information write Dr. Frederick Blodgett, Secretary, Grace-New Haven Community Hospital, Howard Avenue, New Haven, Conn.

The **Tenth Annual Post-Graduate Seminar for Pediatricians** will be presented at St. Christopher's Hospital for Children by the Pediatric Department of Temple University's School of Medicine in Philadelphia, May 24 to 27, 1961. Principal emphasis will be on recent developments in pediatric endocrinology and metabolic disturbances.

For information regarding enrollment, registration, fee, etc., write to Dr. John B. Bartram, St. Christopher's Hospital for Children, 2600 N. Lawrence Street, Philadelphia 33, Pa.

The Pediatric Department of Memorial Hospital for Cancer and Allied Diseases announces their annual course in **Pediatric Oncology** for pediatricians, general practitioners, and health officers to be held April 26 to 28, 1961. The faculty will include 20 members of the Attending Staffs of Memorial Hospital and Sloan-Kettering Institute for Cancer Research. The class is limited to 15 and the fee is $35.00. For information contact Chairman, Department of Pediatrics, Memorial Hospital, 444 East 68th Street, New York 21, N. Y.

The National Vitamin Foundation is sponsoring a one-day symposium on **Mechanisms of Gastrointestinal Absorption** under joint sponsorship of The Johns Hopkins University, School of Hygiene and Public Health, and The National Vitamin Foundation at the Hotel Sheraton-East, New York, at 9:00 A.M. on March 7, 1961. Advance registration is requested; there is no registration fee. For information write Robert S. Goodhart, Scientific Director, 149 East 78th Street, New York 21, N. Y.

Applications for the **Residency in Pediatric Oncology** at Memorial Hospital for Cancer and Allied Diseases in New York City from Jan. 1, 1962, to Dec. 31, 1962, will be received up to May 5, 1961. This residency is approved for partial credit by the American Board of Pediatrics and is limited to the neoplastic diseases of children. The salary is $3,600 annually plus maintenance. For application forms and information write Chairman, Department of Pediatrics, Memorial Hospital for Cancer and Allied Diseases, 444 East 68th Street, New York 21, N. Y.

The **Fourth International Congress of Allergology** will be held at the Hotel Commodore, New York City, October 15 to 20. At the main meetings there will be simultaneous interpretation of all papers in English, French, German, and Spanish. Physicians registering are invited

to present communications which will be grouped in sections according to subject.

Registration fee for regular members will be $45.00, for wives $20.00. For additional information contact Dr. William B. Sherman, 60 East 58th Street, New York 22, N. Y.

The Department of Pediatrics of the University of Wisconsin School of Medicine will present a **postgraduate seminar** April 13 to 15 on **Blood Disorders in Infancy and Childhood** at the University of Wisconsin Center Building. The faculty will include Dr. Louis K. Diamond, Harvard University School of Medicine; Dr. Eugene Lahey, University of Utah College of Medicine; Dr. Irving Schulman, Northwestern University School of Medicine; Dr. Memee King and Dr. Nathan J. Smith, University of Wisconsin School of Medicine; Dr. William Zinkham, Johns Hopkins University School of Medicine; and Dr. Wolf W. Zuelzer, Wayne State University School of Medicine.

Registration is limited to 100 and fee is $50.00. For further information write the Office of Postgraduate Education, University of Wisconsin School of Medicine, Madison 6, Wis.

A **continuation course in pediatrics** will be given at the University of Minnesota Medical School February 27 to March 1. It will include symposia on platelets, the effect of diet and environment in children, and a general discussion of advances in pediatrics, as well as case presentations. Josef Warkany, M.D., will present the McQuarrie Lecture on congenital malformations.

Further information will be furnished by the Department of Pediatrics, The Medical School, University of Minnesota, Minneapolis 14, Minn.

EDITOR'S COLUMN

Psychiatry and the Tower of Babel

THE JOURNAL previously has had occasion to chide our psychiatric brethren for the obscure, unintelligible jargon they have developed, or perhaps retreated into, in their writings in recent years. Occasionally these seemingly fulfill the old cliché of a diarrhea of words and a constipation of thought. The existing situation was summarized unintentionally, although quite succinctly, in a conversation with one of the younger psychiatrists, when he remarked that half the men in his department did not know at times what the other half were talking about.

While a number of our leading psychiatrists have been critical of the unintelligible use of the English language by many of their colleagues, no criticism has been quite so devastating and to the point as the recent remark of the President of the British psychiatrists at a conference at the meeting of the B.M.A. in Torquay in June, that the psychiatrists "are as 'mixed up' as the people they seek to help," and that they dwell in "a new Tower of Babel." To quote from the account in the *London Daily Telegraph and Morning Post* of June 25 (and the venerable *Times* carried a similar version), "'The main object of words,' said Dr. Strauss, 'is to communicate something. Words should have the same meaning everywhere. It is unfortunate that clinical psychiatrists have not been able to evolve a common language.'" To this we would add particularly a language understandable by all other medical men, as has been developed in other special fields. Until this takes place, the psychiatrists themselves cast a shadow on the claim of psychiatry as one of the fundamental medical disciplines. Certainly psychiatrists are not more erudite than other medical men—we grant them greater flights of imagination—and the use of muddled, obscure language is quite the opposite of superior intelligence.

As most of our older readers will know, Chapter 11 of Genesis tells the tale of how Jehovah became incensed at the descendants of the patriarch Noah for their presumption in attempting to build a tower to reach the heavens, and in punishment caused each of them to speak a different tongue—thus the "Tower of Babel." While the comparison of Dr. Strauss refers to the "different tongues" in psychiatry, we might offer for consideration that perhaps there might be an element of punishment involved for the nonsensical presumption advanced by certain psychiatrists that if only there were enough psychiatrists all the personal problems of mankind would be done away with.

Our own criticism of psychiatry and psychiatric language does not stem from an antagonism toward psychiatry or a dislike of psychiatrists for we have had many close friends among the psychiatrists whom we admire and respect, but rather from our great interest in child psychiatry, its future,

and its importance in pediatrics. The names of many—as Kanner—who write and talk in a way we all can understand flash across the mind simply because they "think straight." On the other hand, we seem to be more frequently running across articles in the field of child psychiatry with sentences and paragraphs that are meaningless. Careful rereading and study still leave them meaningless. Perhaps it is our stupidity, but our impression is that the author was simply using words as a parrot and that he himself did not have a clear idea of what he was trying to express. If he did, he should take a course in the English language before attempting to write an article for publication. Not so many years ago in a discussion of a patient with a psychiatrist, he began to use a lot of jargon that was quite confusing and we asked him exactly what he meant by certain words and terms. After a labored and futile attempt to explain, he became so involved that he drew himself up abruptly and said, "*You* would not understand." Perhaps so, but it was quite obvious that he himself did not know clearly what he was saying.

That psychiatry is rather lost and wandering in a dialectic and semantic maze is obvious. More power to the psychiatrists who are analyzing the situation and trying to straigthen out the confused state existing today.

BORDEN S. VEEDER, M.D.

An adult problem—A pediatric challenge?

RECENTLY, a new Height-Weight Standard for adults was published.[1] This Standard was the result of the findings of the *Build and Blood Pressure Study, 1959*, and was based primarily on the comparison of those weights most closely associated with the lowest mortality rates. On the basis of these figures, it is shown that well over one third of the adult population of the United States is overweight, and consequently has an increased mortality rate.[2] The significance of these new adult standards cannot be overemphasized.[3]

In a land of abundance and in a culture that is alert to the merest whim of its children, the overweight child is not unusual. The treatment of the obese child is not only difficult and time consuming but is associated with an unrewardingly high rate of therapeutic failure. It is easy to dismiss the problem by saying that obesity is not associated with an increased mortality rate in children or that the child "will grow out of it." Children do not necessarily "grow out" of their obesity. Eating habits are developed early and are reinforced with each year of life. The fat child too often becomes the fat adult. No branch of medicine has espoused the cause of disease prevention more than has pediatrics.

Perhaps the prevention of adult obesity is more in the hands of the pediatrician than of any other member of the medical profession. It would appear that a reappraisal of the problem of the overweight child in terms of a more aggressive approach is perhaps in order. What the pediatrician does today in this area may well affect the life of the father and mother of the future child of today's pediatric patient.

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